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POIKILOCYTOSIS IN DAIRY CATTLE

J. T. REID, M.S.; C. F. HUFFMAN, PH.D.
AND
C. W. DUNCAN, M.S.
EAST LANSING, MICH.

The term "poikilocytosis" was first used by Quincke [1] in 1880 to designate a pathologic condition of the blood in which variously shaped deformed erythrocytes called poikilocytes appeared. The poikilocytic condition is characterized by various bizarre-shaped erythrocytes which vary greatly in size and shape. The degree of distortion may be extensive or slight, depending on the nature and the severity of the blood disease. Many shapes of poikilocytes have been observed which do not fall into any named class characterized by their particular form. However, various forms and shapes have been described: tailed,[2] filamented,[3] club-shaped,[2c] dumbbell,[4] sickle,[5] spherical,[6] anvil,[4] tennis racquet,[7] stellate,[8] tomahawk or hatchet,[9] gourd,[7a] teardrop,[2b] kidney,[9] cigar,[4] sausage shape,[2b] horseshoe,[7a] oat shape,[2b] dagger,[7a] pencil,[4] target,[10] dimpled,[6a] and boot shaped.[2b]

There are no reports in the literature which indicate that poikilocytosis is a primary disease in itself, and no uniform explanation accounts for the formation or the presence of the poikilocytes in the blood. A number of theories have been proposed, however: (*a*) Arneth (cited by Kanellis [1b] and Haden [11]) expressed the belief that poikilocytes are produced in the bone marrow; (*b*) Isaacs,[12] Cunningham,[4] Dameshek [10b] and Sydenstricker [13] were in agreement on the hypothesis that the cells are "congenitally deformed;" (*c*) according to Osler,[3d] they are produced by an altered condition of the serum, whereas (*d*) Penati [14] and Emmel [3a] favored the belief that erythrocytes are transformed to poikilocytes in the circulating blood.

Bohrod [15] indicated, however, that there is an accentuation of the eccentricity of the elliptic cell after its removal from the body which explains the formation of this type of malshapeness after exposure to the atmosphere. Whether or not this theory explains the production of poikilocytes, it necessitates caution in handling the blood specimen. Other investigators [16] have also suggested the necessity of careful technic in the manipulation of the blood sample in order

From the Departments of Dairy and Agricultural Chemistry and the Institute of Nutrition, Michigan State College.

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1. (*a*) Quincke, H. I., cited by Osler,[3d] vol. 3, p. 882; (*b*) Kanellis, E. S.: Folia haemat. **35**:65, 1927.

2. (*a*) Kracke, R. R.: Diseases of the Blood and Atlas of Hematology, ed. 4, Philadelphia, J. B. Lippincott Company, 1941, p. 95. (*b*) Osgood, E. E., and Ashworth, C. M.: Atlas of Hematology, San Francisco, J. W. Stacey, Inc., 1937, p. 90. (*c*) Kernkamp, H. C. H.: Technical Bulletin 87, Minnesota Agricultural Experiment Station, 1932.

3. (*a*) Emmel, V. E.: Arch. Int. Med. **20**:586, 1917. (*b*) Takeuchi, K.: Folia haemat. **34**:259, 1927. (*c*) Rossle, R.: ibid. **34**:281, 1927. (*d*) Osler, W.: Diseases of the Blood and Blood Glandular System: A System of Practical Medicine, Philadelphia, Lea Brothers & Co., 1885.

4. Cunningham, R. S., in Nelson's New Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1941, vol. 4, p. 3.

5. (*a*) Cooley, T. B., and Lee, P.: Am. J. Dis. Child. **32**:334, 1926. (*b*) Huck, J. G.: Bull. Johns Hopkins Hosp. **34**:335, 1923. (*c*) Herrick, J. B.: Arch. Int. Med. **6**:517, 1910. (*d*) Sydenstricker, V. P.; Mulherin, W. A., and Houseal, R. W.: Am. J. Dis. Child. **26**:132, 1923. (*e*) Cheney, G.: J. A. M. A. **98**:878, 1932. (*f*) Kracke.[2a] Emmel.[3a]

6. (*a*) Haden, R. L., and Evans, F. D.: Arch. Int. Med. **60**:133, 1937. (*b*) Ponder, E.: The Mammalian Red Cell and the Properties of Haemolytic Systems, Berlin, Verlagsbuchhandlung Gebrüder Borntraeger, 1934, p. 75.

7. (*a*) Da Costa, J. C.: Clinical Hematology, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1905, p. 183. (*b*) Osgood and Ashworth.[2b] (*c*) Cunningham.[4]

8. Whitlock, S. C.: J. Wildlife Man. **3**:14, 1939.

9. Cunningham.[4] Da Costa.[7a]

10. (*a*) Bohrod, M. G.: Am. J. M. Sc. **202**:869, 1941. (*b*) Dameshek, W.: ibid. **200**:445, 1940.

11. Haden, R. L.: Am. J. M. Sc. **188**:441, 1934.

12. Isaacs, R.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1937, vol. 1, p. 5.

13. Sydenstricker, V. P.: J. A. M. A. **83**:12, 1924.

14. Penati, F.: Arch. per le sc. med. **54**:189, 1930.

15. Bohrod, M. G.: Elliptical Erythrocytes: Relation to Crenation, unpublished data, 1941.

16. (*a*) Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942, pp. 51, 67 and 81. (*b*) Osgood and Ashworth.[2b] (*c*) Cunningham.[4] (*d*) Da Costa.[7a]

to avoid confusing the poikilocytes with artefacts. Da Costa [7a] stated that poikilocytosis is akin to crenation so far as the cells in both conditions may be similarly distorted and misshapen. It is unlike crenation, however, for the reason that poikilocytosis is a pathologic condition, demonstrable the moment the blood is withdrawn from the body, whereas crenation is a physical phenomenon dependent on external influences for its production. Crenation never occurs until the blood has remained exposed to the air for some time. Osgood and Ashworth [2b] regarded crenation as an artefact produced by faulty preparation of the blood specimen and stated that the crenated forms may be differentiated from the poikilocytes by the regularly notched outline and nodular surface which are characteristic of all of the cells in a particular area. Kanellis,[1b] Cunningham,[4] and Wintrobe [16a] called attention to the possible confusion of poikilocytes with crenated erythrocytes produced artificially by trauma during the preparation of the blood film. Other physical influences which distort the shape of the red blood cell are: (*a*) diluting the blood sample in saline solution,[17] (*b*) drying blood films slowly,[2b] (*c*) heat,[18] (*d*) hemorrhage [3b] and (*e*) irradiation with roentgen rays.[1b] Different chemical substances have been shown to produce changes in normal erythrocytes resulting in shapes which resemble poikilocytes. Sodium chloride,[19] alkali dissolved from glass,[20] mercuric chloride,[3c] lecithin and cholesterol,[1b] and alanine [21] are some of the substances which will alter the shape of the red cells.

Research on poikilocytes occurring alone in animals is quite limited. Its occurrence in connection with human diseases has been studied in a secondary manner. Little is known concerning its cause and mechanism. However, the appearance of poikilocytes has been observed and described as observed in different species of animals and in human beings not only in disease but also in health. Many workers [22] observed poikilocytes with many bizarre shapes in blood from patients with pernicious anemia. Takeuchi [3b] found filamented red blood cells and detached filaments in 69 per cent of observed cases of tuberculosis, carcinoma, intestinal disorder and fever, in addition to those seen in cases of pernicious anemia. Kilduffe [22a] pointed out that abnormally shaped erythrocytes may appear in any case of severe or long-standing anemia. Elliptic red corpuscles, according to Florman and Wintrobe,[23] are noted in most cases of anemia, and sometimes more than 25 per cent of the cells are affected. Da Costa [7a] reported the general occurrence of small, slightly deformed poikilocytes in milder types of anemia and larger, extremely distorted poikilocytes in the more severe types. Penati [14] associated elliptically deformed erythrocytes with pernicious anemia, secondary anemia and hemolytic icterus, but he found no relationship between the intensity of cell deformation and the severity of the anemia, although the deformed cells became less noticeable with amelioration of the anemia.

Sickle cell anemia (first named by Mason [24] in 1922 but first described by Herrick [5c]) is a condition in which a specific and constant type of poikilocytosis is associated with anemia. Huck,[5b] Sydenstricker [13] and Alden [25] observed the sickle cells in the blood of male and female patients characterized by anemia and a tendency to have ulcers on the legs. Sydenstricker [13] reported sickle cell anemia occurring with abdominal pains and pathologic changes of the spleen. Cells of peculiar sickle shapes were noted in tissue sections and blood films by Landon and Lyman [26] in 1929. According to Emmel,[3a] the sickle cell trait appears to be hereditary and occurs most commonly in the Negro race although the reports of Hunter and Adams,[27] Lawrence [28] and Cooley and Lee [5a] showed the occurrence of this condition in other races. Van den Bergh [29] and Huck [5b] demonstrated that this condition may be inherited by either sex as a dominant trait.

Dameshek [10b] reported a type of anemia characterized by target cells, which constituted as much as 32 per cent of the erythrocytes, and

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18. (*a*) Levy, J.: Arch. Path. **7**:820, 1929. (*b*) Hahn, E. V., and Gillespie, E. B.: Arch. Int. Med. **39**: 233, 1927. (*c*) Ponder, E.: The Erythrocyte and the Action of Simple Haemolysins, Edinburgh, Oliver & Boyd, 1924. (*d*) Koeppe, H.: Arch. f. d. ges. Physiol. **99**:33, 1903. (*e*) Kanellis.[1b] (*f*) Takeuchi.[3b]

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20. Waller, W. W.: J. Physiol. **56**:218, 1922.

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22. (*a*) Kilduffe, R. A.: The Clinical Interpretation of Blood Examinations, Philadelphia, Lea & Febiger, 1931, p. 200. (*b*) Quincke.[1a] (*c*) Kanellis.[1b] (*d*) Takeuchi.[3b] (*e*) Cunningham.[4] (*f*) Da Costa.[7a] (*g*) Isaacs.[12]

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26. Landon, J. T., and Lyman, A. V.: Am. J. M. Sc. **178**:223, 1929.

27. Hunter, W. C., and Adams, R. B.: Ann. Int. Med. **2**:1162, 1929.

28. Lawrence, J. S.: J. Clin. Investigation **5**:31, 1927.

29. Van den Bergh, A. A.: Arch. f. Verdauungskr. **43**:65, 1928.

resembling somewhat Cooley's sickle cell anemia. He designated this condition "target-cell anemia" although this type of cell was found to be associated with other types of anemia. Bohrod [10a] stated that the target cells appear for a short time in acute types of anemia but disappear as the erythrocyte count rises. In chronic types of anemia the target cells exist for a long period in quantities as great as 10 per cent of the erythrocytes. Haden and Evans [6a] observed target cells in several different types of anemia but found them in great numbers in sickle cell anemia. Wintrobe [16a] associated various undifferentiated poikilocytes and target cells with Mediterranean anemia. Isaacs [12] in studies of blood films of patients having miliary lesions of the bone marrow observed abnormal shapes in some of the red blood cells. The presence of poikilocytes in myelogenous leukemia and chlorosis was indicated by Emmel.[3a]

Mrowka [30] reported the presence of red corpuscles of spindle or elliptic shape in the blood of horses suffering from infectious anemia. Poisonous substances elaborated by many helminths were regarded by Hutyra and Marek [31] as a cause of poikilocytosis and anemia. Bernhard [32] reported what he termed "oval poikilocytosis," which was accompanied by anemia and a splenic tumor. Apinis [33] observed filamented red blood cells in the blood of horses, cattle, sheep, dogs, cats, rabbits, pigs and chickens. The filaments varied for different animals in a distinctive manner. Thin filaments were noted on the erythrocytes of hogs, very long filaments on those of chickens and button-like structures on those of sheep and cats, and granulation was noticeable in the red blood cells of the horse. He gave no description of the erythrocytes observed in the blood of cattle. O'Roke [24] and Whitlock [8] observed sickle cells, stellate cells, rod-shaped cells and other poikilocytes in the blood of deer. Hanke and Koessler [34] reported poikilocytes in the blood of guinea pigs showing symptoms of scurvy. The observation of spindle-shaped poikilocytes in fowl's blood was made by Gordon.[35]

Vawter [36] made microscopic examinations of the blood of dairy cattle and found poikilocytosis associated with anaplasmosis. He concluded that this is one of several clinical findings which distinguish anaplasmosis from bacillary hemoglobinuria (or red water disease) in dairy cattle. Blount [37] noted a few sickle cells in the blood of a day old calf which he thought were artefacts. He observed no poikilocytes in the normal adult bovine animal. Neal and Ahmann [38] reported that anisocytosis and poikilocytosis were observed in their studies of anemia in dairy calves of Florida. Knoop and others [39] showed a photomicrograph of a blood smear from a milk-fed calf with severe anemia which demonstrated extensive poikilocytosis.

From a review of the literature it is obvious that only limited studies have been made of poikilocytosis in bovine animals. The object of this paper is to report the occurrence and the symptoms of poikilocytosis and the association of the condition with health and disease of dairy animals receiving various farm rations.

PROCEDURE

Calves of different ages representing Holstein, Guernsey, Jersey and Ayrshire breeds, cows representing Holstein, Guernsey and Jersey breeds, 5 cows with fistula of the rumen in the herd of the Michigan State College and dairy animals in herds on farms of Michigan were used in this investigation. The major portion of the data, however, was derived from calves in the experimental herd of the Michigan State College.

The animals in most cases were bled weekly and often several times during the week. Jugular blood was used for microscropic examination, hemoglobin determinations and other tests employed in the investigation. All blood samples except those used for microscopic examination were collected in test tubes containing lithium citrate as the anticoagulant. Since several authors have indicated that contamination with certain reagents and faulty manipulation in preparing a specimen for examination may result in artefacts which resemble the poikilocyte, all known precautions were employed to avoid these errors. Only freshly shed blood was used since the common anticoagulants are salts capable of increasing the osmotic pressure sufficiently to effect possible alterations of shape. Immediately after the blood was drawn, a small drop was placed on a clean side, spread over its surface with a clean coverslip and dried as rapidly as possible.

Some hanging drop preparations were made also as a check on the blood smears, with an isotonic solution of sodium chloride or blood plasma being used as the suspension medium. A few drops of blood were drawn through a paraffin-lined rubber tube attached to a paraffin-lined bleeding needle which was submerged below the surface of the suspension medium contained in a receptacle. This apparatus prevents direct contact of the blood with the atmosphere. The blood was mixed in the medium and the hanging drop was prepared and sealed in a depression slide for microscopic examination.

30. Mrowka, F.: Vet. Bull. **6**:174, 1935.
31. Hutyra, F., and Marek, J.. Special Pathology and Therapeutics of the Diseases of Domestic Animals, Chicago, Alex Eger, 1926, vol. 2, p. 339.
32. Bernhard, G.: Klin. Wchnschr. **6**:1493, 1927.
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35. Gordon, L.: Virchows Arch. f. path. Anat. **262**: 1938, 1926.
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37. Blount, W. P.: Vet. J. **95**:222, 1939.
38. Neal, W. M., and Ahmann, C. F.: J. Dairy Sc. **30**:741, 1937.
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Weekly hemoglobin determinations were made by the method of Sanford, Sheard and Osterberg.[40] Standard procedures were employed for the blood cell count and the determination of cell volume.

RESULTS

Incidence of Poikilocytosis.—During the course of this investigation the blood from 423 animals was studied, 190 of which showed no evidence of poikilocytosis. The number and the percentage of animals affected with poikilocytes and the percentage of poikilocytes in the blood are shown in table 1. In 78 animals the poikilocytes constituted more than 51 per cent of the total red blood cells; in 53 animals, more than 61 per cent; in 44, more than 71 per cent; in 32, more than 81 per cent, and in 14, more than 91 per cent.

TABLE 1.—*Distribution of Given Degrees of Poikilocytosis in Affected Animals*

Percentage of Poikilocytes, Range	Affected Animals	
	Number	Percentage
1 - 10	81	34.7
11 - 20	31	13.2
21 - 30	21	9.0
31 - 40	13	5.5
41 - 50	19	8.1
51 - 60	15	6.8
61 - 70	9	3.8
71 - 80	12	5.1
81 - 90	18	7.8
91 -100	14	6.0
Total	233	100.0

TABLE 2.—*Incidence of Poikilocytosis in Three Different Herds in One Community*

Animal	Percentage of Poikilocytes	Hemoglobin Content, Gm. per 100 Cc.	Red Blood Cell Count
	Unaffected Herd		
R1	0	13.7	.....
R2	0	12.5	.....
R3	0	11.2	7,840,000
R4	0	12.5	.....
R5	0	10.1	.....
R6	0	11.7	.....
R7	0	12.8	6,940,000
R8	0	11.3	.....
R9	0	10.9	.....
R10	0	10.5	.....
	Affected Herds		
N1	78	10.5	8,380,000
N2	95	11.4	8,100,000
N3	95	11.6	.....
N4	50	11.6	.....
T1	50	14.3	7,480,000
T2	65	13.3	.....
T3	95	10.5	10,100,000

It was observed that one or more herds in a community would tend to show a high incidence of poikilocytosis while the neighboring herd or herds would be entirely free from this condition. Table 2 shows data on two herds with poikilocytosis and an unaffected herd in the same community.

Biconcave Disk-Shaped Erythrocytes.—The microscopic observations of the blood smears from the 423 animals reveal that 190 had normal biconcave disk-shaped erythrocytes. Symmetric regularly outlined round corpuscles with transparent-appearing centers suggesting biconcavity were noted. By the use of the hanging drop preparation, in which the erythrocytes could be observed from many different angles, it was found that the predominant shape of the erythrocytes in normal, healthy dairy cattle is the biconcave disk. Figure 1 shows a photomicrograph of a blood smear of a representative animal showing the normally shaped red corpuscles.

Poikilocytes.—Almost all of the shapes of the poikilocytic cells described in the literature were observed in this study. In addition, many other bizarre forms were seen to which no descriptive name has been applied. The most prevalent poikilocyte encountered consists of a "body" of variable shape and size from which tail-like structures protrude. The tail-like protrusions varied from 2 to 7 microns in length. The number of tails per cell commonly varied from one to five and were arranged in a haphazard fashion around the body of the cell. Frequently, cells possessing a round "body" were observed to have one or two of the protruding structures. The tail-like structures were a definite part of the cell and were stained homochromically with the rest of the cell. The severity of the poikilocytic condition seemed to be associated with the length of the tail-like protrusions. Figure 2 is a photomicrograph of a blood smear showing many shapes of poikilocytes in the blood of a representative animal.

Many other shapes suggestive of the following objects were seen: urn, half moon, star, oval cell, sickle, tear drop, pipe, horseshoe, kidney, tennis racquet, Christmas tree, gondola, tomahawk, dagger, oat, sausage and gourd. All of them often appeared with tail-like or filamented structures identical with those already described. The degree of distortion of cell and irregularity of shape was more accentuated in the bloods that contained the larger numbers of poikilocytes. The extreme contrasting appearance of normal erythrocytes and severely poikilocytic cells is best illustrated by an examination of figures 1 and 2.

Cells with Crenation Induced by Hypertonic Saline Solution.—It was observed early in this

40. Sanford, A. H.; Sheard, C., and Osterberg, A. E.: Am. J. Clin. Path. **3**:405, 1933.

investigation that the possibility of confusing poikilocytes with crenated corpuscles was slight. Crenation induced in normally shaped corpuscles with 2 per cent saline solution is manifested by a somewhat symmetric and regular arrangement of nodular or short spinelike structures around the periphery of the corpuscle when viewed in a blood smear. In hanging drop preparations this phenomenon was seen on the surface of the corpuscle as well as at the periphery. A comparison of the poikilocytes in figure 2 with the crenated forms in figure 3 evidences this observation. The crenated shapes in figure 3 are those induced in the normal corpuscles shown in figure 1 with 2 per cent saline solution. The regular arrangement of nodules and other features of

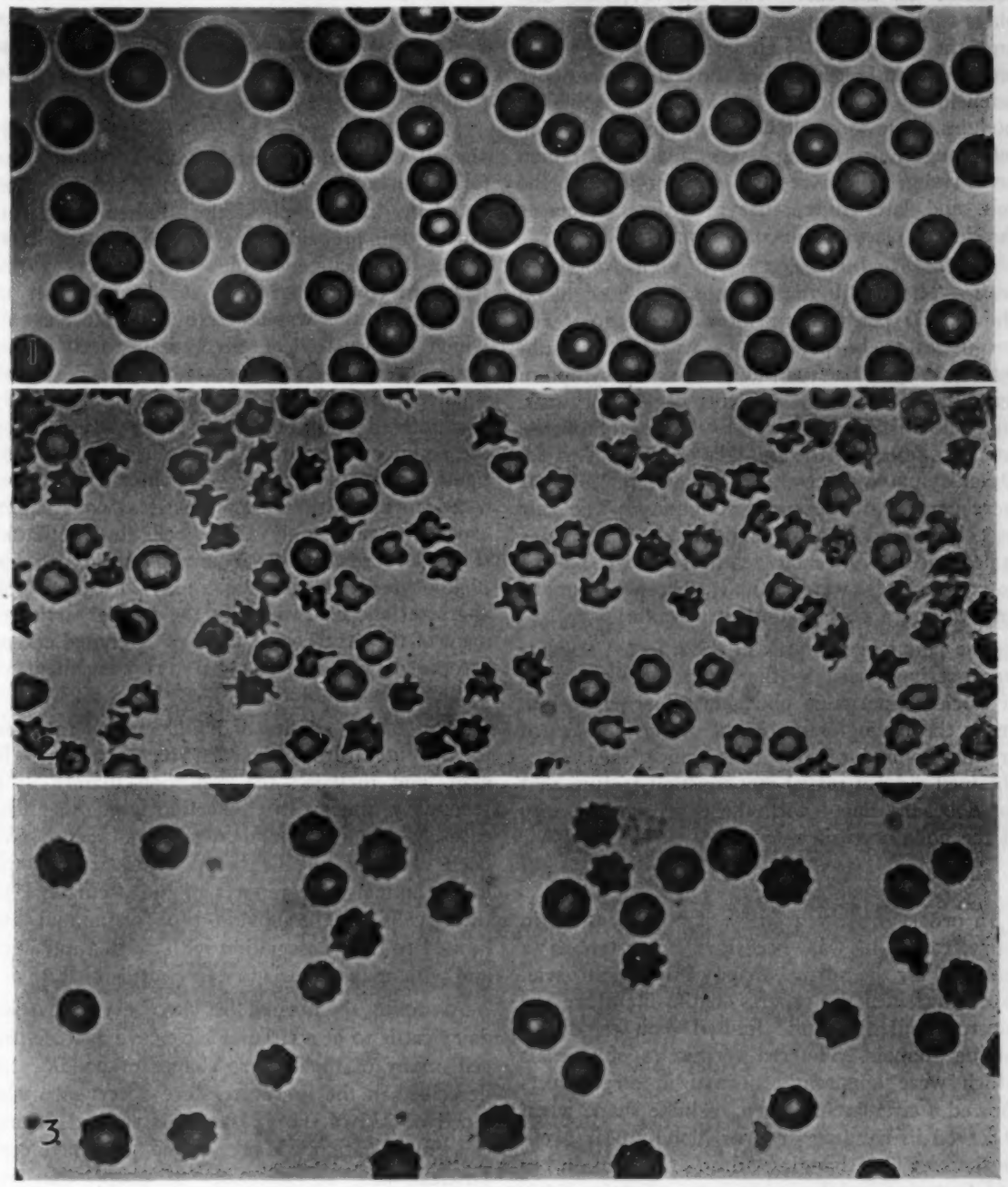


Fig. 1.—Photomicrograph of a blood smear showing normal bovine biconcave disk-shaped erythrocytes; × 1,270.

Fig. 2.—Photomicrograph of a blood smear showing poikilocytic cells; × 1,270.

Fig. 3.—Photomicrograph of a blood smear showing crenated cells produced from the same normal corpuscles shown in figure 1; × 1,270.

the crenated forms offer a sharp contrast to the different bizarre forms exhibited by the poikilocytes in figure 2.

Several stages of crenation were observed which were apparently due to the severity of the process. In the early stage the corpuscle displays slight wrinkling and bulging of the surface and the periphery. Later in the process the wrinkled and bulged foci of the cell become more intensified in the form of knobs or spinelike nodules. These structures appear to develop into longer, protruding coarse filaments, which are arranged in a regular fashion around the cell, and later finer, fuzzy, hairlike processes develop in place of the coarser protrusions.

Health of Animals Affected with Poikilocytosis.—The health of the animals whose blood showed 50 per cent or more of the total red corpuscles to be poikilocytes was usually subnormal. Anorexia was the outstanding symptom that accompanied high incidence of poikilocytosis. In some instances, however, depraved appetite was manifested by the animal's chewing of wood. Other symptoms shown by the affected animals were general thinness and roughness. The hair was long and shaggy and had a hard, dry appearance. Noticeable features shown by the young animals were a marked retardation of growth and a general unthrifty condition.

The poikilocytic status of the affected animals was not influenced by the plasma concentration of calcium, inorganic phosphorus or magnesium or by the hemoglobin content or the number of or the volume of red cells, since the values obtained did not reveal any constant feature that could be associated with the degree of severity of the poikilocytosis.

COMMENT

In order to make a study of poikilocytosis in dairy cattle it was necessary to establish a standard for the normal shape of the erythrocyte, especially since the reports in the literature are controversial and quite limited with regard to bovine animals. The red corpuscles of animals which were apparently normal in all respects showed a circular biconcave disklike shape when observed in hanging drop or blood smear preparations. The hanging drop preparation in which the corpuscles were suspended in either isotonic solution of sodium chloride or blood plasma was particularly adapted to the study of corpuscular shape "in vitro" since it permitted the observation of the corpuscle from many different viewpoints. The stained red cells in blood smears showed a round, regular outline and a heavily stained rim at the periphery of the cell with a light or nonstaining inner portion, suggesting a biconcave disk shape as the normal erythrocyte shape. No investigation has definitely established the normal in vivo shape of the bovine erythrocyte, and the studies of the normal shape in vitro are also recorded in a somewhat contradictory manner. The form observed in this study, however, is in close agreement with the bovine corpuscular shape described by Blount.[37]

Many investigators have shown that normally shaped corpuscles manifest alterations in conformation as a result of having been contaminated by different physical and chemical agents during the preparation of the blood specimen. Since the occurrence of such artefacts would result in confusion in the study of cell shape, every precaution was taken to avoid those agents which are capable of effecting changes in the shape of the cells. Crenated corpuscles were reported [41] to be the artefacts most commonly encountered and those most nearly resembling the poikilocytes. It was found during this investigation that the chances of confusing the crenated forms with the poikilocytes were slight, especially since only those cells in the latter stages of crenation bear any similarity to the poikilocytes. The outstanding distinguishing characteristic observed was the regular arrangement of the protrusions from the crenated cell as compared with the haphazard arrangement of those of the poikilocyte.

Most of the studies of poikilocytosis reported in the literature concerned its occurrence in man, and included the condition mainly as a secondary interest in connection with other diseases. Although the deformed red cells have been observed in the blood of several of the lower animals, the reports of the occurrence of these cells in the bovine type of animal are limited to their association with anemia in calves and with anaplasmosis in dairy cattle.

Assuming the normal "in vitro" erythrocyte of dairy cattle to be a circular biconcave disk-shaped cell, many of the bizarre shapes of poikilocytes described in the literature were observed in the blood of 233 of the 423 animals studied during this investigation. Many of the deformed corpuscles were so irregular in shape that no particular name could describe them. The majority of the poikilocytes observed in the blood of the animals severely affected with the disease were generally classifiable in the latter nondescript group of poikilocytes. Deformed cells classed in this category consisted of a

41. Osgood and Ashworth.[2b] Da Costa.[7a]

body portion from which pseudopodium-like processes protruded which gave the poikilocyte a striking configuration. The degree of cell distortion seemed to be correlated directly with the severity of the condition, the erythrocytes of more severely affected animals manifesting the greater deformation. This observation is in agreement with Da Costa's [7a] finding that the blood of human beings shows poikilocytosis.

In a given vicinity it was found that one entire herd would manifest the condition while a neighboring herd would be completely unaffected. The condition appeared rather widespread, and the incidence of affected animals was high—55.1 per cent of the total number of animals studied.

Although an occasional mature animal manifested poikilocytosis, the young animals and the calves were more frequently affected. Usually health was subnormal in animals whose blood showed 50 per cent or more of the total corpuscles as poikilocytes, and at least 1 animal showed unthriftiness when only 35 per cent of the cells were poikilocytes.

The blood pictures of the affected animals failed to disclose any item that could be associated constantly with poikilocytosis. Anisocytosis appeared frequently in the blood of animals with normal erythrocytes as well as in the blood of those showing poikilocytes and was, therefore, not considered of any consequence. Although the photomicrographs published by Knoop and co-workers [39] indicated the occurrence of poikilocytosis in association with severe anemia in calves, the present investigation revealed that the hemoglobin content, the red blood cell count, the red blood cell volume and the average corpuscular hemoglobin values were independent not only of the incidence of poikilocytosis but also of the degree and severity of cell distortion. The hemoglobin content of the blood of the affected animals ranged from 4.4 to 15.9 Gm. per hundred cubic centimeters of blood. The blood of the animal which had the lowest hemoglobin value showed only 25 per cent as many poikilocytes as the animal whose blood had the highest hemoglobin value. It was observed, however, that many of the animals whose blood had a low hemoglobin concentration showed the presence of poikilocytes but that not all of the animals affected with poikilocytosis had a low concentration of hemoglobin in their blood.

In this study observation was made of some dairy herds manifesting poikilocytosis while neighboring herds were unaffected. Since the rations fed to these animals varied greatly in kind and quality, it is assumed that the presence of poikilocytes in the blood was to a large extent attributable to a nutritional deficiency. Some of the dietary factors involved in the control of poikilocytosis in dairy cattle will be presented in a subsequent paper.

SUMMARY

Dairy cattle ranging from young calves to mature cows were used in a study of the occurrence and the symptoms of poikilocytosis.

The normal erythrocytes of dairy cattle "in vitro" have a circular biconcave disk shape when observed from a surface view and have the appearance of a dumbbell when observed from an edge view.

The possibility of confusing poikilocytes with the artefacts produced in crenation is negligible.

The distribution of poikilocytes among the 233 affected animals varied up to more than 91 per cent of the red corpuscles (see table 1).

The symptoms manifested by the animals with severe poikilocytosis were: anorexia, thinness, unthriftiness, a dry and harsh condition of the hair coat and, in young animals, a retarded rate of growth. Depraved appetite was frequently observed.

The occurrence of poikilocytosis in dairy cattle is independent of the hemoglobin content, the number and the volume of red blood cells and the calcium, inorganic phosphorus and magnesium contents of the blood.

EXPERIMENTAL REPRODUCTION OF MADUROMYCOTIC LESIONS IN RABBITS

DOUGLAS SYMMERS, M.D.
General Director of Laboratories, Department of Hospitals, City of New York
NEW YORK

Up to the present time (1945) twenty-two species of fungi belonging to ten genera and four families have been implicated in the production of the various types of maduromycosis. In spite of this multiplicity of causes, the different types clinically may resemble one another closely, and in some instances they may also resemble actinomycosis, especially if the latter disease is confined to a lower extremity as is maduromycosis in many cases. Clinically, cases of maduromycosis may be divided into three groups. In all of them the lesions are limited to the part which was originally infected, as the foot, the hand, the knee, the neck or the face. Unlike the changes one finds in actinomycosis, the deeper viscera seem never to become involved, nor does it appear that maduromycosis has been encountered in cattle or other lower animals. In one group of cases the changes are confined to superficial structures in the form of granulomatous lesions of the skin or of the skin and the subcutaneous tissues. In a second group of cases there are one or more circumscribed fibrous, fatty or, occasionally, cystic nodules, usually without ulceration of the overlying skin. In 1 case belonging to this group a solitary tumor-like growth on the dorsum of the foot had been present for eighteen years. The third, and perhaps the commonest variety, is characterized by the presence of multiple subcutaneous nodules varying in diameter from one to several centimeters. These nodules are movable, painless and nontender. Spontaneously, or sometimes as the result of injury, the superficial nodules rupture and discharge mucopurulent material containing white, yellow or black granules, the color of the granules depending on the type of fungus concerned. Finally, the affected part becomes riddled with sinuses which penetrate muscle, fat and even bone.

Symmers and Sporer [1] have shown that there is a series of distinctive histologic changes in a variety of black grain maduromycosis which is caused by the presence in the tissues of a fungus composed of septate and branching mycelial filaments and chlamydospores, the latter predominating. They described three types of granuloma of different degrees of maturity occurring in the midst of cellular and well vascularized granulation tissue which is richly infiltrated by foam cells. The youngest granulomas consist almost exclusively of clumps of brownish black chlamydospores embedded in accumulations of polymorphonuclear neutrophilic leukocytes. The older granulomas are more or less sharply circumscribed by connective tissue, and most of them are arranged around collections of multinuclear giant cells containing phagocytosed necrotic chlamydospores. In the case recorded by Symmers and Sporer efforts to cultivate the fungus on various artificial mediums were continued over a period of several months but were unsuccessful. The object of the present paper is to note the results of subsequent successful efforts to cultivate the causative fungus from the tissues of the same patient and to describe the changes produced by inoculating the subcutaneous tissues of rabbits with black grains freshly removed from the patient's hand and with the fungus that was grown on artificial culture medium. The patient from whom the fungus was isolated was a white man aged 67, a clerk, who stated that in 1935, two years before admission to the hospital, he fell and scraped his right hand on an old and partially decayed wooden floor, "picking up many splinters." Two or three weeks later, the right hand became swollen, and multiple pustules appeared with black dots in them. At the time of the patient's admission the hand was greatly swollen and showed many nodular formations on both the palmar and the dorsal aspect. Some of these nodules contained sinuses which discharged yellowish pus containing black granules. The causative fungus was recently identified by Dr. C. W. Emmons [2] as an organism which was first described by Langeron [3] in 1928 under the name of

From the Laboratories of Pathology, Goldwater Memorial Hospital.

1. Symmers, D., and Sporer, A.: Arch. Path. **37**: 309, 1944.

2. Emmons, C. W.: Personal communication to the author.

3. Langeron, M.: Ann. de parasitol. **6**:385, 1928.

Torula jeanselmei and was isolated from maduromycosis of the foot. However, Dr. Emmons regards the fungus as a species of Phialophora and transfers it to that genus under the designation of Phialophora jeanselmei.

EXPERIMENTAL INOCULATION OF RABBITS

Granules of fungus that had been freshly removed from the hand of a patient with maduromycosis or that had grown after inoculation on artificial culture medium (Sabouraud's agar with 6 per cent dextrose and liver extract) were crushed in sterile salt solution and injected into the subcutaneous tissues of rabbits just below the level of the interscapular fat pads. This method of introduction was selected in order to duplicate as nearly as possible the route followed by the fungus when man is infected through the skin by pricks of contaminated thorns or as the result of other superficial and apparently trivial injuries. Each rabbit was inoculated on only one occasion and at one point only, although liberal quantities of fungus were distributed through the point of injection into different areas covering a radius of 4 or 5 cm. It was thought that local reactions would occur resulting in the formation of multiple nodules corresponding to the places where the fungus had been deposited. In this regard the results were disappointing. The injected granules seemed invariably to gather at a common point so that in each rabbit only a single nodule occurred. The nodules were excised, with the animal under local anesthesia, at intervals varying from three to one hundred and twenty-six days. The tissues were fixed in 4 per cent formaldehyde solution and embedded in paraffin. Microscopic examination showed essentially the same changes as those described by Symmers and Sporer in a variety of human maduromycosis. As in man, the lesions in the rabbit consisted of localized granulomas of different degrees of maturity displayed against a background of moderately well vascularized and cellular or irregularly sclerotic granulation tissue. In those nodules which followed injections of fungus directly removed from the patient, the granulation tissue contained great numbers of foam cells, and the granulomas were formed around necrotic and fused chlamydospores together with occasional necrotic mycelial filaments, thus duplicating the histologic changes described by Symmers and Sporer in the tissues of a human patient with maduromycosis. On the other hand, in those nodules which were produced experimentally in rabbits by the artificially grown fungus, the granulomas were formed around apparently well preserved mycelial filaments and chlamydospores.

Reifenstein, Ferguson and Weiskotten[4] have shown that in physiologic circumstances the lymphocyte is the prevailing cell in the rabbit's blood, polymorphonuclear neutrophils occurring in relatively small numbers. Eosinophils are present in practically the same numbers as in the blood of man. From this it follows as a matter of no surprise that the earliest inflammatory changes in experimental maduromycotic lesions in rabbits are attended by preponderant exudation of lymphocytes, although in both the acute exudative and the chronic productive inflammatory lesions it is astonishing to note how often there are great numbers of eosinophils.

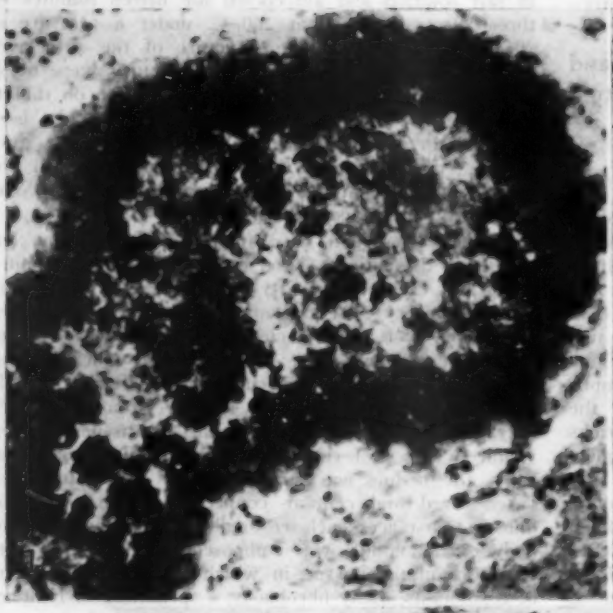
For purposes of comparison, rabbits were inoculated with artificially grown fungus that had been suspended in salt solution and autoclaved for fifteen minutes on three successive days at 260 C. under a pressure of 20 pounds (9 Kg.). The structure of the autoclaved fungus appeared to be intact, and cultures were negative. During that period of experimentation on rabbits when it was desired to inject granules that had been removed directly from the patient and killed by autoclaving, no granules were available because all the sinuses in the patient's hand were closed and had apparently healed completely.

Granules that had been freshly removed from the sinuses in the patient's hand were injected into rabbit 1 April 26. On June 23, fifty-eight days after this injection, a solitary subcutaneous nodule had attained the size of 0.7 by 0.3 by 0.3 cm. The nodule was elevated above the surface of a fat lobule to which it was attached and was well circumscribed. It was faintly yellowish and speckled with black. Occasional black specks lay free in the surrounding fat tissues without visible evidence of reaction around them. Microscopically, the nodule was surrounded by moderately well vascularized and cellular connective tissue, which in one or two places enclosed small lymph follicles. The body of the nodule was composed of irregularly sclerotic granulation tissue in which there were numbers of eosinophils, many fibroblasts, a sprinkling of lymphocytes, innumerable foam cells and circumscribed granulomas in different stages of maturity. The youngest granuloma was made up of collections of dark brown, degenerate and clumped chlamydospores, along the edges of which were pinkish-staining short projections representing necrotic mycelial remnants, the whole embedded in collections of lymphocytes, polymorphonuclear neutrophilic leukocytes and eosinophils, many of them necrotic (fig. 1). In other parts of the nodule there were numbers of rounded or oval mature granulomas which were encapsulated by fibroblastic connective tissue, enclosing variously sized clumps of similarly pigmented and necrotic chlamydospores and numbers of eosinophils. In some of the encapsulated, mature granulomas there were multinuclear giant cells, which showed phagocytosed chlamydospores in their cytoplasm (fig. 2). In other words, histologically, both the nonencapsulated, immature and the encapsulated, mature granulomas were practically identical with the same sort of granulomas which occur in the tissues of human patients with maduromycosis.

Two cubic centimeters of a suspension of living, artificially grown fungus was injected into rabbit 2 June 7. The animal died three days later. At necropsy there were two small clumps of blackish material near the point of injection. The tissues in the immediate vicinity appeared to be edematous. Otherwise necropsy revealed nothing of note in the present connection. Microscopic examination showed several large and small, rounded, oval or irregularly outlined clumps of brownish, apparently well preserved fungus surrounded by mantles of lymphocytes. Beginning encapsulation was indicated by the presence of a delicate but incomplete layer of fibroblastic connective tissue (fig. 3). The granulation tissue in the immediate proximity of most of the granulomas was edematous and contained scattered collections of fungus with no indication of reaction around them.

Two cubic centimeters of a suspension of living, artificially cultivated fungus was injected into rabbit 3 June 6. June 21, fifteen days after the injection, a nodule measuring 0.5 by 0.5 by 0.5 cm. was removed from the subcutaneous tissues. It was freely movable and sharply circumscribed. On section the center of the nodule was composed of whitish, glistening firm

4. Reifenstein, G. H.; Ferguson, J. H., and Weiskotten, H. G.: Am. J. Path. **17**:219, 1941.



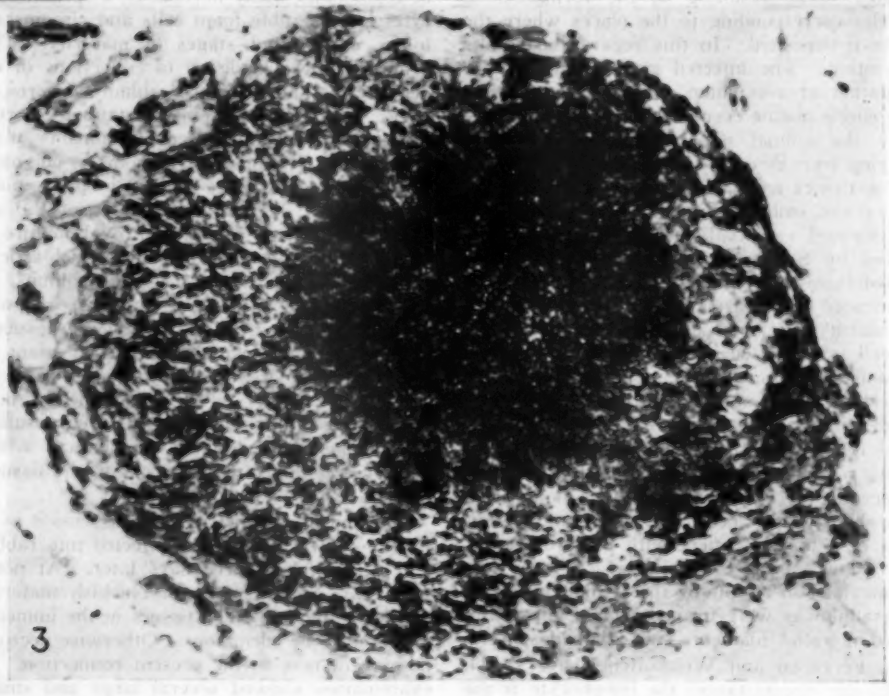


Fig. 1.—Photomicrograph of an immature granuloma showing an irregularly outlined clump of pigmented chlamydospores and, at the periphery, numerous lightly staining short projections representing necrotic mycelia, the whole embedded in a matrix of leukocytes. From rabbit 1, inoculated with black granules freshly removed from a patient with maduromycosis of the hand; hematoxylin and eosin; paraffin section; × 396.

Fig. 2.—Photomicrograph showing two mature granulomas with clumped and pigmented chlamydospores. The lower granuloma is almost completely encapsulated and shows multinuclear giant cells with phagocytosed chlamydospores. From rabbit 1 inoculated with black granules freshly removed from a patient with maduromycosis of the hand; hematoxylin and eosin; paraffin section; × 200.

Fig. 3.—Photomicrograph of an immature granuloma showing a central collection of chlamydospores, short mycelia at the periphery and an admixture of lymphocytes. From rabbit 2 inoculated with living, artificially grown fungus; hematoxylin and eosin; paraffin section; × 316.

tissue while the periphery was light brown and numerous minute black specks were visible in it. Microscopic examination showed an edematous and delicate fibrillar connective tissue capsule. At one side of the nodule, immediately under the capsule, were large collections of lymphocytes scattered through which were clumps of brownish, apparently well preserved fungous cells. To the inner side there was a large field made up of granulation tissue which in places was richly vascularized by thin-walled capillary blood vessels lying in collections of eosinophils and moderate numbers of lymphocytes. In other places the granulation tissue was traversed by intercommunicating bands of poorly cellular, occasionally hyalinized connective tissue surrounding islands made up of capillary blood vessels, numerous eosinophils and a few lymphocytes. In one part there was a large granuloma which was circumscribed by fibrillar connective tissue. The body of the granuloma was made up of a central collection of eosinophils, while in the immediate vicinity was a solitary multinuclear giant cell rimmed at one edge by a layer of brownish phagocytosed fungous cells (fig. 4). Lying free in the tissues of the granuloma was a small mass of apparently well preserved fungus. In still other places the granuloma contained several nonnucleated large protoplasmic bodies representing, probably, immature giant cells.

A suspension of living, artificially cultivated fungus was injected into rabbit 8 June 6. July 10 it was noted that there was a freely movable nodule immediately beneath the skin near the point of injection. The nodule measured approximately 0.5 cm. in length and was blackish. The mass was removed August 2, fifty-seven days after the injection. On removal the nodule was oval, measured 1 by 0.4 by 0.4 cm. and was speckled with black. It was surrounded by a smooth, glistening capsule. In the immediate vicinity were several minute black granules which lay free in the tissues without any obvious reaction around them. Microscopically, the nodule was surrounded by a thin capsule of mature connective tissue. The body of the nodule was made up of numerous large and small clumps of fungus consisting of apparently well preserved brownish chlamydospores and short segmented and occasionally branching mycelial filaments, likewise brownish, lying among masses of necrotic lymphocytes.

Large quantities of a suspension of living, artificially grown fungus were injected September 26 into rabbit 12. January 30, one hundred and twenty-six days later, a subcutaneous nodule was removed. It measured 0.8 by 0.8 by 0.4 cm., and, on section, was composed of an outer smooth whitish hyaline layer and a core of yellowish granular material, each measuring about 0.2 cm. in thickness. No black granules were visible to the unaided eye. Microscopically, the outer part of the nodule was composed of thick hyalinized connective tissue, beneath which there were large numbers of fibroblasts and foam cells. Frozen sections stained with sudan IV showed numerous fat globules in the cytoplasm of many of the fibroblasts and in all of the foam cells; the latter cells were obviously derived from the former. The center of the nodule was composed of necrotic lymphocytes, among which were variously sized clumps of apparently well preserved fungous cells lying free or enclosed in the cytoplasm of multinuclear giant cells.

Large quantities of artificially grown fungus which had been suspended in salt solution and killed by autoclaving were injected into rabbit 6 June 28. July 1 a quantity of blackish tissue measuring 0.6 by 0.4 by 0.3 cm. was removed. Microscopically, it was composed of variously sized collections of well preserved brownish fungous cells embedded in large accumulations of lymphocytes. In some of the serial sections there was a solitary immature small granuloma which contained a central collection of fungous cells surrounded by a mantle of lymphocytes and, at the periphery, by a delicate layer of fibrillar connective tissue, the whole corresponding histologically to the youngest form of granuloma encountered in human maduromycosis and to the experimentally produced granuloma in rabbit 2.

A suspension of killed fungus was injected into rabbit 11 July 28. September 20, fifty-four days later, a nodule was removed which measured 1 by 1 by 0.3 cm. The nodule was covered by a filmy connective tissue capsule and was freely movable; it was mottled in pink, black and yellow, lobulated, tense in consistency and flattened. Microscopically, it was surrounded by an irregularly vascularized fibrillar connective tissue capsule. The body of the nodule was composed almost exclusively of rather large rounded cells with poorly chromatic, vesicular nuclei and pinkish-staining granular or finely reticulated cytoplasm, morphologically suggesting foam cells in miniature. They were divided into islands of irregular shapes and sizes by intercommunicating bands of moderately well vascularized connective tissue. In many of the islands, groups of eosinophils were to be seen with or without polymorphonuclear neutrophilic leukocytes. Others enclosed collections of apparently well preserved brownish fungous cells (fig. 5). In still others, groups of calcified chlamydospores were present.

COMMENT

One of the advantages of reproducing human disease in lower animals is to provide a means for experimental methods of treatment. It is believed that the histologic changes in that form of maduromycosis which is due to Phialophora jeanselmei have been sufficiently faithfully reproduced in rabbits to furnish an acceptable approach for the use of experimental methods of therapy. In this form of maduromycosis the granules that are discharged from the sinuses in diseased tissues as well as the colonies which grow on artificial culture mediums are composed of apparently well preserved mycelial filaments and chlamydospores. In microscopic preparations of diseased tissues the morphologic aspect of the fungus is noticeably changed, the organism occurring almost exclusively in the form of disintegrated chlamydospores. Mycelia, if present at all, are practically always necrotic. When granules are removed directly from the discharging sinuses of the patient and are injected subcutaneously into rabbits, the fungus appears in the rabbits' tissues in the form of similarly disintegrated chlamydospores with or without necrotic mycelia. On the other hand, when the artificially grown fungus is injected into rabbits, the structure of the fungus remains apparently unchanged. In those instances in which the organism is destroyed in the tissues, it is not evident whether destruction follows devitalization or whether the reverse is true. However this may be, it is ob-

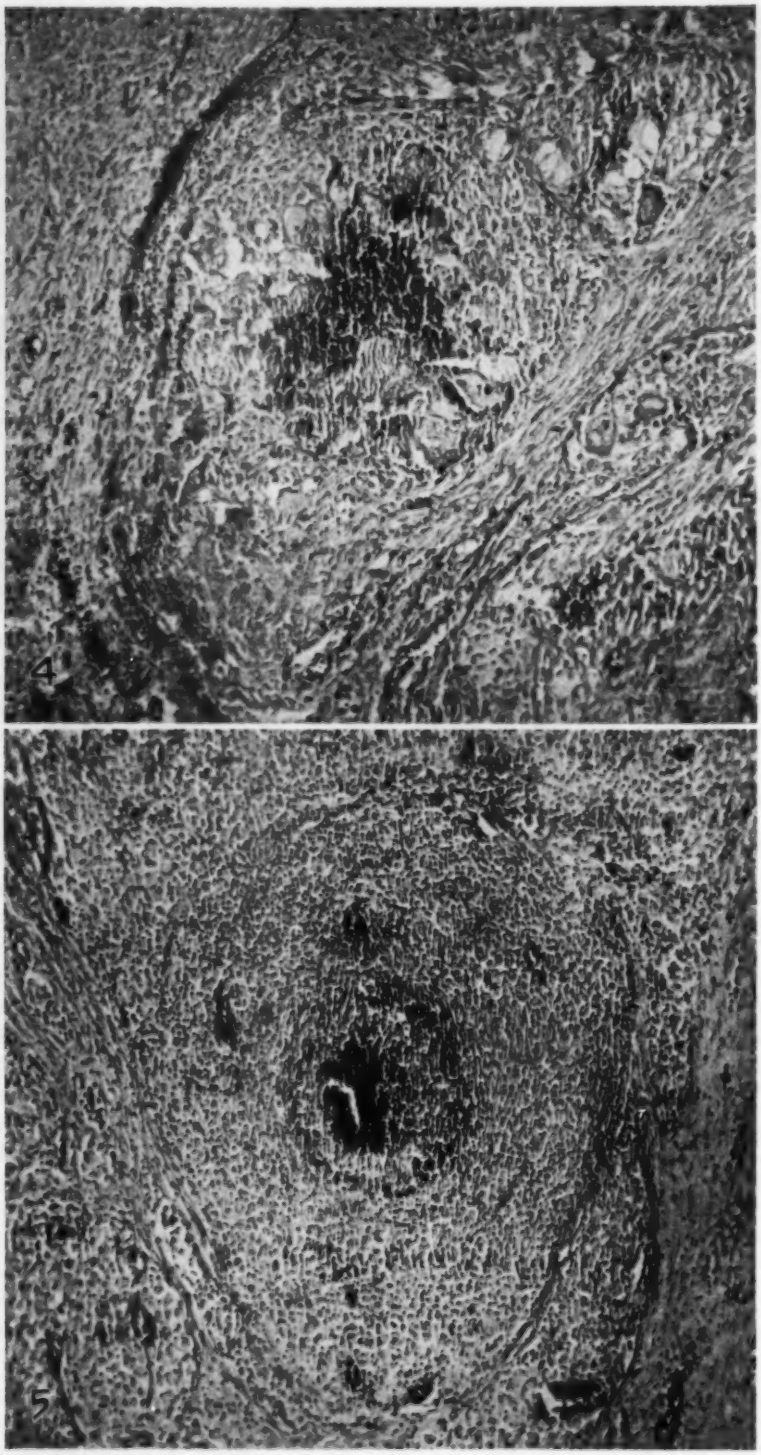


Fig. 4.—Photomicrograph showing mature, encapsulated granulomas. The partially circumscribed granuloma at the left contains a large central collection of eosinophils and at the lower right a multinuclear giant cell rimmed below by phagocytosed fungous cells. From rabbit 3, inoculated with living, artificially grown fungus; hematoxylin and eosin; paraffin section; × 135.

Fig. 5.—Photomicrograph showing a solitary, partially encapsulated, mature granuloma. At the center is a clump of fused fungous cells lying in a collection of eosinophils. The greater part of the body of the granuloma is composed of lightly staining cells suggesting miniature foam cells. From rabbit 11, inoculated with killed, artificially grown fungus; hematoxylin and eosin; paraffin section; × 90.

vious that in order to determine experimentally the value of any therapeutic agent for use in this form of maduromycosis the source of the fungus must be known; that is to say, whether it is derived from diseased tissues or from artificial culture mediums.

In approaching the treatment of maduromycotic lesions in experimentally infected rabbits it seems logical to attempt first to learn the effect of various supposedly injurious agents on the fungus in vitro. It has already happened several times in my experience that the fungus remained alive and its structure apparently intact after prolonged exposure to substances of this description. In another instance the fungus remained morphologically intact but had apparently been devitalized, since it could not be grown subsequently on artificial culture mediums. At all events, these are the general lines of procedure that are now being followed in efforts to determine the value, if any, of various substances in the treatment of experimentally produced maduromycotic lesions in rabbits.

CONCLUSION

Phialophora jeanselmei when injected subcutaneously into rabbits produces solitary nonulcerative nodules which histologically are specific and are closely comparable to the nodules in that form of maduromycosis in man which is caused by the same fungus.

PHIALOPHORA JEANSELMEI COMB. N. FROM MYCETOMA OF THE HAND

C. W. EMMONS, PH.D.
Principal Mycologist, United States Public Health Service
BETHESDA, MD.

The term "mycetoma" was proposed by Carter [1] to designate fungous infections of the subcutaneous tissues characterized by swelling, formation of sinuses and production of pus in which there are well organized mycotic granules. The granules differ in size, shape, hardness and color and in the morphology of the constituent hyphae, as Carter [2] pointed out. As additional cases were investigated it became apparent that although the cases had certain clinical characteristics in common actually there are several types of mycetoma, depending on the identity of the etiologic agents. The relationships of several species of fungi to cases of mycetoma were elucidated by Brumpt,[3] and Pinoy [4] proposed a division into the actinomycoses caused by species of Actinomyces and Nocardia, and the "true mycetomas" caused by fungi of several unrelated genera having in common only the characteristic of larger hyphae than are found in Actinomyces. Chalmers and Archibald [5] substituted the name "maduromycosis" for "true mycetoma," and this name has been used widely. Some writers, however, have used it as a synonym of "mycetoma" without recognizing the distinction made by Chalmers and Archibald.

The choice of the name "maduromycosis" to designate the latter group of "true mycetomas" is perhaps unfortunate because of the derivation of the word and the heterogeneity of the tumors in the group. According to Carter,[2] Colebrook introduced into scientific literature the name "Madura foot," by which mycetoma of the foot was locally known near Madura, India, and Brumpt [3] created the name Madurella for a fungus causing it. It is apparent, however, from Carter's reports that from the earliest studies a multiple causation was recognized and that species of Nocardia were among the fungi causing Madura foot. Subsequently the term "Madura foot" has been used rather loosely to designate mycetoma of the foot in cases of diverse geographic origin and cause. Nine species of Madurella have been described, and besides these there are species in several other genera which cause similar tumors of the foot. The latter fungi appear to be mycologically unrelated to Madurella (which may be itself a heterogeneous aggregation), and the lesions they cause are not all like those of the originally described Madura foot. It may be questioned whether the term "maduromycosis" designates this heterogeneous group any more conveniently than the original name, "mycetoma." Neither term is precise, and both require supplementary labeling as to etiology in order to convey information about the true nature of a given case. If "maduromycosis" is used it should be used in the restricted sense and not as a synonym of "mycetoma."

Gammel [6] summarized more recent knowledge about the fungi causing the tumors grouped as mycetoma and described as new two species which he had studied. He remarked that mycologic knowledge about the fungi causing mycetoma was meager. Unfortunately, this is still true, owing in part to the fact that adequate mycologic studies have not been made in many cases, and in part to the fact that these fungi sometimes grow abnormally on agar culture mediums, not revealing their actual mycologic relationships. These fungi need to be restudied with special attention to the variability of strains and the correct interpretation of abnormal or equivocal structures. This may make it possible, on the one hand, to reduce to synonymy some of the many species names now associated with these infections and, on the other, to determine the relationships between genera in which these species

From the Division of Infectious Diseases, National Institute of Health.

1. Carter, H. V.: Tr. Med.-Phys. Soc. Bombay (1861) **7**:206, 1862.
2. Carter, H. V.: Tr. Med.-Phys. Soc. Bombay (1860) **6**:104, 1861.
3. Brumpt, E.: Arch. de parasitol. **10**:489, 1906.
4. Pinoy, E.: Bull. Inst. Pasteur **11**:929 and 977, 1913.
5. Chalmers, A. J., and Archibald, R. G.: Ann. Trop. Med. **10**:169, 1916.
6. Gammel, J. A.: Arch. Dermat. & Syph. **15**:241, 1927.

are now placed. Recent observations[7] have shown, for example, that Allescheria boydii is the ascocarpic form of Monosporium apiospermum (one of the most frequent causes of mycetoma in the United States). The relationship between these two forms had been suspected, but direct proof of it had not been presented previously.

Symmers and Sporer[8] recently reported a case of mycetoma of the hand. The fungus was isolated by Symmers and used by him in experimental inoculation of rabbits, as reported in a paper[9] accompanying this one. The fungus is unlike those isolated in most cases of mycetoma. However, it resembles closely a fungus which was described as Torula jeanselmei by Langeron[10] after its isolation in a case of mycetoma reported by Jeanselme, Huet and Lotte.[11] The clinical changes in the latter case closely resembled those reported by Symmers and Sporer except that the foot rather than the hand was involved. In both cases the granules were unlike those seen in most instances of mycetoma. They were relatively small, many being hollow with irregular interruptions of the wall, as shown in sections (figs. 3 and 4 of Symmers and Sporer, and figs. 2 and 6 of Langeron). Chlamydospores were conspicuous features of the granules in both cases. In most cases, on the contrary, the granule is firm, with a relatively dense structure composed of radiating hyphae. Exceptions have been listed by Langeron. Clinical and histologic similarities in themselves are not conclusive evidence that the 2 cases had a common etiologic factor. It is generally conceded that the fungus causing mycetoma in any case can be identified only after its isolation in pure culture. The characteristics of the fungus isolated from the patient observed by Symmers and Sporer correspond closely to those of the fungus which Langeron described. This fact, together with the clinical and pathologic similarities, has led to the conclusion that the two strains are identical.

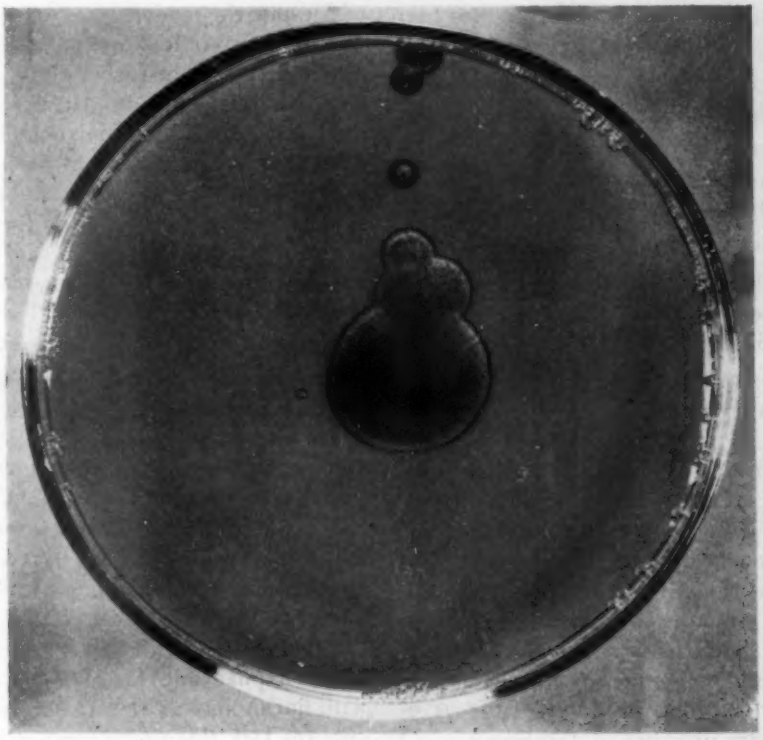


Fig. 1.—A colony of Phialophora jeanselmei comb. n. grown on modified Sabouraud's agar.

The fungus described in this paper when grown on modified Sabouraud's agar (Difco neopeptone 1 per cent, chemically pure dextrose 2 per cent) produces a colony which is dome shaped, with an entire margin, reaching a diameter of 22 mm. and a height of 5 mm. after two weeks' growth at 30 C. (fig. 1). The color is

7. Emmons, C. W.: Mycologia **36**:188, 1944.
8. Symmers D., and Sporer, A.: Arch. Path. **37**: 309, 1944.
9. Symmers, D.: Arch. Path., this issue, p. 358.
10. Langeron, M.: Ann. de parasitol. **6**:385, 1928.
11. Jeanselme, Huet and Lotte: Bull. Soc. franç. de dermat. et syph. **35**:369, 1928.

"deep grayish olive." [12] The surface is covered with delicate short aerial hyphae, giving the colony a fine plushlike appearance.

On glycerin agar slants after two weeks at 30 C. a colony 1 to 1.5 mm. wide appears along the line where spores were deposited at the time of inoculation, and colonies reaching a diameter of 5 mm. develop where larger pieces of inoculum lodged. These colonies are nearly black and appear at first glance to be glabrous, but careful examination with a lens shows numerous coremia or tapering hyphal aggregations rising from the surface. The growth on horse meat infusion agar is similar. In gelatin after two weeks' growth at 30 C. minute colonies develop at the bottom of the tube, but no liquefaction has been observed.

The fungus grows poorly on corn meal agar. Some transfers failed to make any visible growth, and others developed into very small, black, nearly glabrous colonies, almost microscopic in size. No growth was apparent after two weeks at 30 C. on glycerinated potato plugs and litmus milk. Indole was not formed.

Growth was better at 30 C. than at either room temperature or 37 C.

Microscopic examination reveals dark-colored septate hyphae varying in diameter from 1 to 3 microns (fig. 2 *A* to *F*). Many hyphae, especially those which first develop, are toruloid (fig. 2 *G* to *I*). The conidiophores are tubular (fig. 2 *A, B, E* and *F*) or flask shaped (fig. 2 *C* and *D*) and stand at an angle of 90 degrees or less from the vegetative hyphae. Many are single and unbranched, but others are branched and may occur in groups. Some are tubular and of nearly uniform diameter to a point near the distal end, where they taper to a narrow tip (fig. 2 *A, B, E* and *F*). Others are urn shaped, tapering toward both the base and the tip (fig. 2 *C* and *D*). In some cases the tip extends into a flaring cup (fig. 2 *C*). The dimensions of the conidiophores are too variable to be of much value in identifying the fungus, but the tubular conidiophores are usually 1 to 3 microns in diameter and 5 to 15 microns long. In addition to the morphologically well differentiated conidiophores, many hyphae bear conidia laterally on very short rudimentary conidiophores (fig. 2 *E*), which in many cases are little more than pegs or apiculate knobs on the hyphal walls. In some cases this method of sporulation recalls that found in Pullularia pullulans.

12. Ridgway, R.: Color Standards and Color Nomenclature, Washington, D. C., The Author, 1912.

On all of the types of conidiophores described here the conidia are borne at the tip. They are pushed out serially through an opening at the end of the conidiophore, where they collect in a group held together by some adhesive substance. The conidia are hyaline or subhyaline, elliptic, and about 0.75 to 1 by 1 to 2 microns in size. Conidia which are borne at the agar surface or which come into contact with it continue to grow, reaching a size of 2 to 3 by 4 to 5 microns or larger. The walls of these large conidia contain the same brown pigment which colors the hyphae and the conidiophores. When conidia at the agar surface increase in size, they usually bud in a yeastlike manner to form secondary conidia.

Despite the tendency of conidia to cluster about the tips of conidiophores it is apparent that when the mycelium is disturbed some conidia are readily discharged from it. If, in transferring a culture, one picks up a portion of dry sporulating mycelium and attempts to place it at the center of an agar plate, spores almost invariably are dropped along the way from the edge to the center of the Petri dish (fig. 1). The actual mechanism of this spore discharge has not been determined.

In attempting to identify this fungus one is struck at once by the resemblance of a colony to that of Phialophora verrucosa, an etiologic agent of chromoblastomycosis. The color of a colony grown on modified Sabouraud's agar is practically identical with that of a colony of the latter fungus but the rate of growth is slower, and this slow rate of growth is even more apparent on corn meal, Czapek's and glycerin agars. There is also a microscopic resemblance between the two species with respect to the brown vegetative hyphae and the urn-shaped conidiophore with flaring mouth. However, most of the conidiophores lack this phialoform structure for which the genus was named. It may be mentioned incidentally that this structure is also poorly developed or sometimes lacking in some other species of the genus isolated from wood and originally described as species of Cadophora. Despite a superficial resemblance to P. verrucosa the fungus can be differentiated easily from that species by the greater variability of its conidiophores, the somewhat smaller size of the young conidia, a greater tendency of the conidia to produce secondary conidia and its poor growth on certain mediums already mentioned, on which P. verrucosa grows readily. Furthermore, P. verrucosa grows in human tissue in the form of chlamydospores aggregated at most into small clusters, whereas this fungus forms granules a millimeter

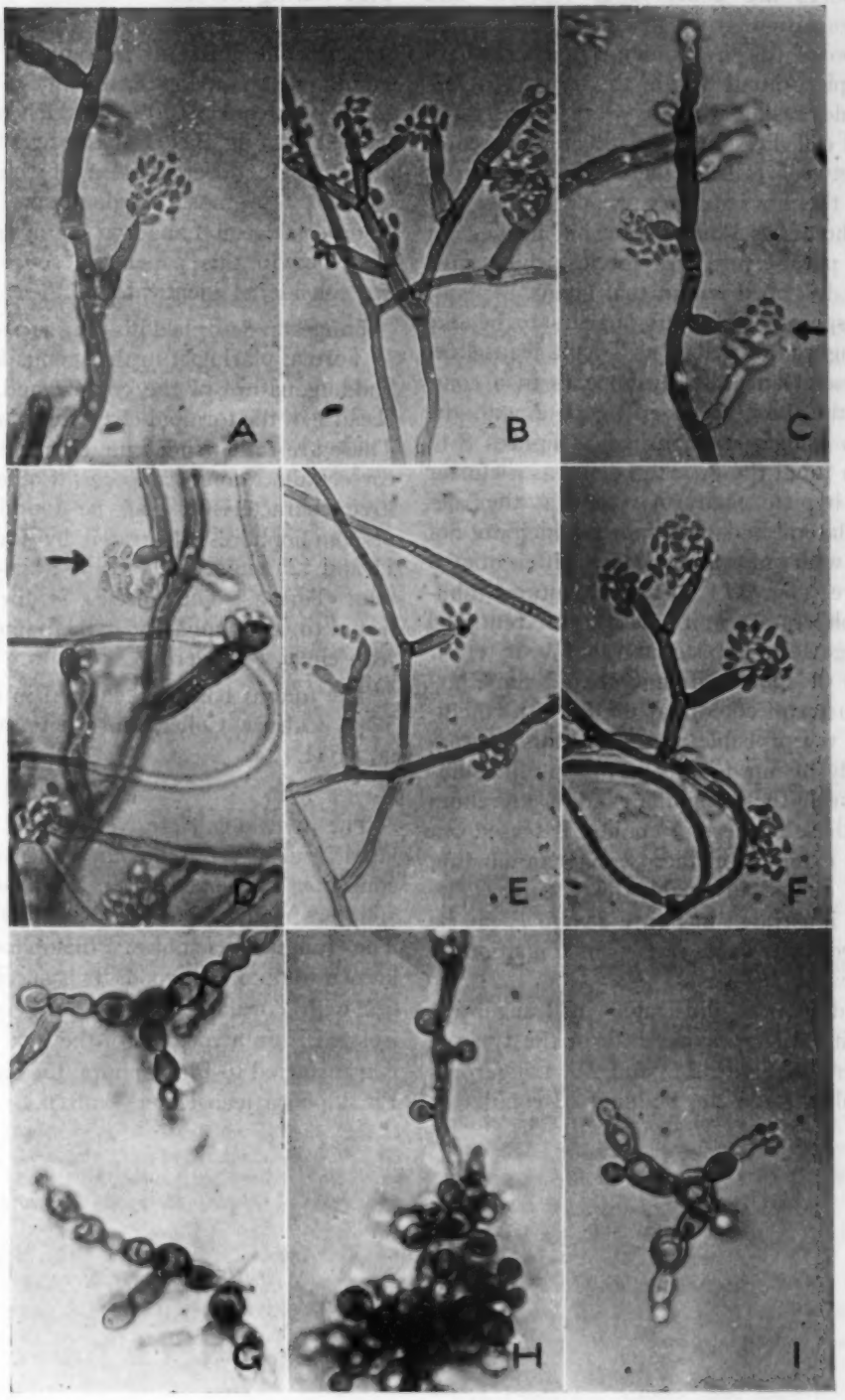


Fig. 2.—Various appearances of Phialophora jeanselmei. In *C* and *D* arrows indicate the two types of conidiophores observed—that discharging conidia through a flaring cuplike structure and that discharging them through a short tubelike extension.

or two in diameter. It can be pointed out, however, that in these granules in both species chlamydospores are conspicuous features and that the transition from a cluster of several chlamydospores (as in chromoblastomycosis) to a macroscopic granule (as in this type of mycetoma) would result if there were more rapid growth and cell division and a greater degree of adhesion between cells in the case of the larger granule. It therefore appears proper to place this fungus in the genus Phialophora, but it does not correspond precisely to any species which have been found described within that genus.

In all respects the fungus appears to be like the one Langeron described as Torula jeanselmei and this resemblance clearly appears in a comparison of the illustrations in figure 2 with the illustrations Langeron published as figures 8 to 12. In both fungi the growth begins as a cluster of toruloid hyphae, many of which, as they develop, bear lateral buds and spores which are not associated with morphologically differentiated conidiophores (fig. 2 *I*). In older cultures tubular conidiophores are more clearly differentiated from the vegetative hyphae, and they bear terminal clusters of spores. Langeron did not illustrate the cluster of conidia at the tip of a conidiophore, but the probable reason for this appears from a study of our fungus. There is little adhesion between these conidia, and if mycelium containing these clusters of conidia is teased out in the usual manner for microscopic examination the conidia almost invariably float away. The relationship illustrated in figure 2 *A* to *F* can be demonstrated only by a careful examination of slide cultures.

The conidiophores illustrated in Langeron's figures 11 and 12 are apparently of the type illustrated here in figure 2 *C* and *D*. Langeron's figure 12a illustrated the budding of conidia to form secondary conidia, which is commonly seen in our strain. He did not illustrate conidiophores with flaring mouths. Although a rare conidiophore of this type, bearing an expanded apical structure, as illustrated in figure 2 *C*, was found in our strain, many have only a very delicate tubular extension through which the spores are pushed out (fig. 2 *D*), and there is little apparent morphologic differentiation of this type at the fertile tip of most conidiophores. The resemblances between Langeron's fungus and the one described in this paper are so close that they are considered identical.

Langeron described his fungus as a new species of Torula, placing it in that genus because of the budding nature of the conidia and, presumably, because of the toruloid character of many hyphae. These are rather indefinite characteristics for the correct allocation of a species if other more definitive characteristics can be found. The types of conidiophores illustrated by Langeron (figs. 11 and 12) suggest the genus Phialophora rather than Torula. The species is therefore transferred to that genus under the name Phialophora jeanselmei (Langeron) comb. n.

The fungus has been entered in the American Type Culture Collection, where it is listed as no. 9541.

SUMMARY

The mycologic characteristics of a fungus isolated from mycetoma of the hand are given. The condition developed after an injury in which splinters from a wooden floor pierced the skin. The fungus resembles Phialophora, which is known to occur on wood. It is specifically identified with Torula jeanselmei Langeron which was isolated from mycetoma of the foot. This species is transferred to Phialophora, the name becoming Phialophora jeanselmei comb. n.

ACUTE AGRANULOCYTOSIS

A MICROSCOPIC STUDY OF ULCERONECROTIC GINGIVA AND OF BONE MARROW IN A CASE

CAPTAIN GEORGE J. ANDAY
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
BALINT ORBAN, M.D., D.D.S.
CHICAGO

Gingivitis and stomatitis are among the earliest and most common symptoms of agranulocytosis. Necrotic ulcers occurring at the margins of the gingiva are frequently encountered. Jackson, Parker, Rinehart and Taylor [1] observed oral lesions in each of 13 patients whom they studied. Lichtenstein [2] reported 27 cases of agranulocytosis, in 17 of which there were oral lesions. Reviewing 43 cases from the literature, Kastlin [3] noticed an inflammatory process of the oral lining in all cases and necrotic ulcers of the gingiva in 9. The early appearance of gingivitis is remarkably well demonstrated in a case of recurring agranulocytosis observed by Cook [4]; each of his patient's four subsequent attacks started with gingivitis. For compiled data on oral lesions in agranulocytosis the reader is referred to the comprehensive reviews by Appleton,[5] Cahn,[6] Epstein,[7] Hanzlik [8] and Watkins,[9] as well as to the standard textbooks on dentistry.

Despite their frequency, histologic examination of gingival lesions is almost entirely lacking. Most reports mention only the gross lesions. Those reports containing histologic data usually give a general description of the necrotic lesions of the entire oral or oropharyngeal lining without specific reference to the gingiva. One of the most lucid histologic descriptions of a necrotic ulcer on the posterior pharyngeal wall is that of Ophüls, of forty-three years ago, reported in the frequently quoted paper of Brown.[10] Several similar descriptions have been recorded since the clinical picture of agranulocytosis was described by Schultz in 1922. Apart from the characteristic necrosis, lack of polymorphonuclear leukocytes and edema, little attention was paid to the differences in the cellular reaction of the tissues around the lesion. In Brown's [10] report the zone of infiltration around the necrosis was said to consist mostly of "epitheloid" cells, some lymphocytes and few polymorphonuclear leukocytes. A few similar cells but no particular zone of reaction was observed around the oropharyngeal lesions by Lovett,[11] Kastlin [3] and Rotter.[12] Marked lymphocytic and plasma cell infiltration was present around the necrosis in a case reported by Rotter [12] (tonsils) and in Plum's [13] cases ("neck organs"). Petri [14] observed in extensive ulcerations of the gastrointestinal tract lymphocytes, some histiocytes, plasma cells and large "lymphocyte-like" cells.

The present histologic study was made on a biopsy specimen of the gingiva in a case of acute agranulocytosis. The advantages of a fresh biopsy specimen for finer histologic study are evident. Nevertheless, only one reference to a biopsy of the gingiva in the literature appears to be available, that of Bernier,[15] although a detailed analysis of his case is lacking. As far

From the Department of Medicine, Loyola University School of Medicine (Captain Anday) and the Research Department of the School of Dentistry of Loyola University, Chicago College of Dental Surgery (Dr. Orban).

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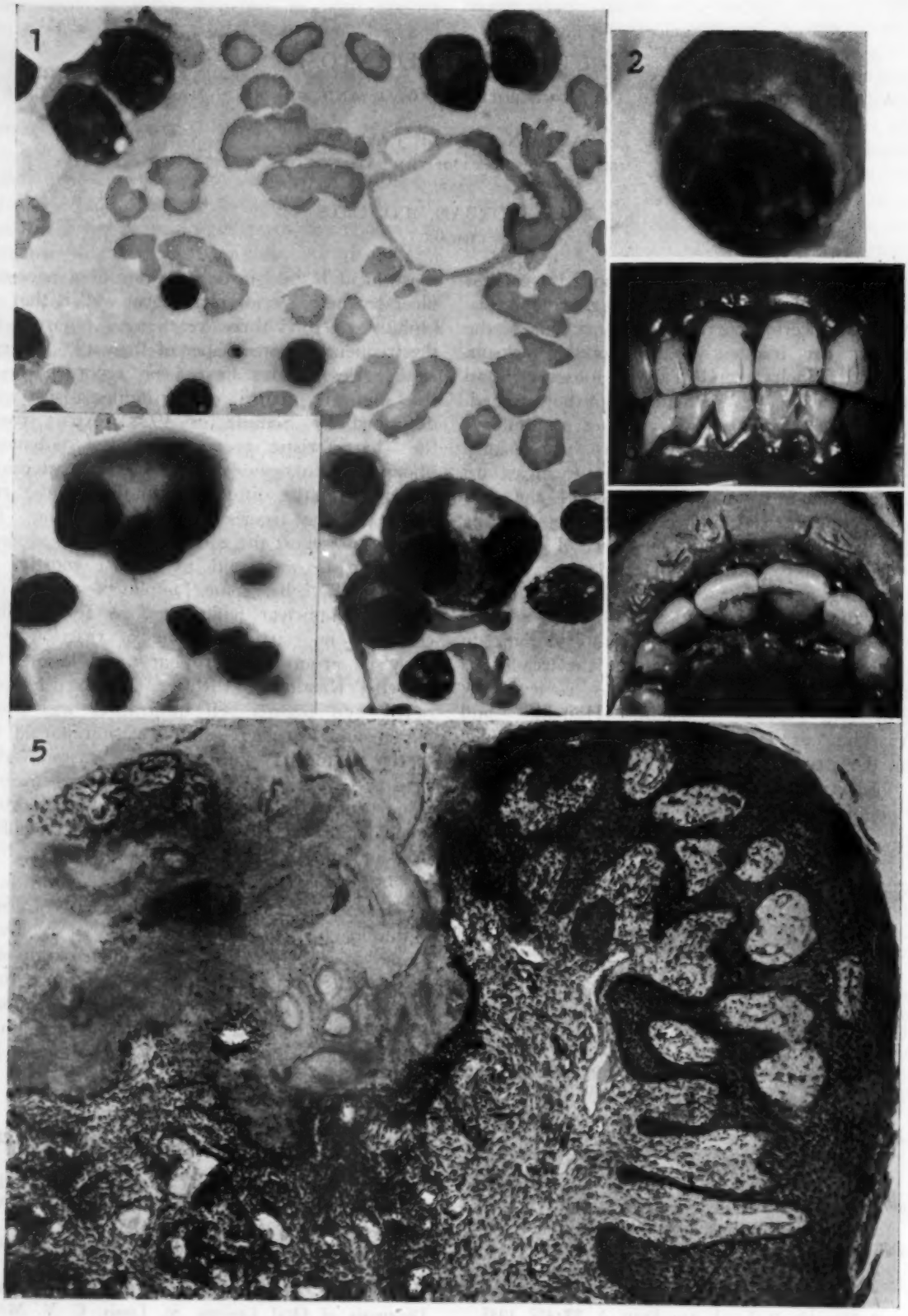

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as could be ascertained, no other biopsy or detailed study of such a gingival lesion has been reported in the medical or the dental literature.

REPORT OF A CASE

The case is one of those that were not recognized at an early stage of the disease. A 26 year old woman was admitted to a hospital with high fever and in a critical condition. For the preceding two weeks she had been treated for "flu" and "trench mouth." She had taken some drugs for the "flu," but she could give no information as to what drugs or the amount. The first blood count was made on admission. At the same time the routine examinations were made, and for differential diagnosis a biopsy specimen of one of the smaller ulceronecrotic lesions was obtained and a sternal puncture was made. In smears from the gingival lesions, mostly fusiform bacilli and Vincent's spirochetes were seen. Blood transfusions and injections of pentnucleotide were given. However, after a brief declining course the patient died.

At admission the blood revealed moderate anemia with 2,900 white cells. The differential count showed 1 per cent eosinophils, 1 per cent basophil polymorphonuclear leukocytes, 83 per cent lymphocytes, 9 per cent monocytes and 6 per cent Türk cells. Two days later a second count showed a decrease in the white cell count to 1,050, with a complete absence of polymorphonuclear leukocytes; the differential count showed 92 per cent lymphocytes, 5 per cent monocytes and 3 per cent Türk cells. The red blood cells were normal in size and shape, and the platelets were normal in number and appearance.

Microscopic examination of the marrow (obtained by sternal puncture) revealed large numbers of plasma cells. Their basophilic cytoplasm contained a darker stained outer and a lighter stained inner zone. Vacuoles in the cytoplasm were frequent. The nucleus was eccentric and had the typical cartwheel structure. The plasma cells varied greatly in size, from 10 to 22 microns, and many were binucleated and frequently arranged in groups (fig. 1); some were trinucleated (fig. 1, inset).

Large phagocytic reticulum cells with an ill defined, light blue-stained cytoplasm and large, round nuclei were present, frequently in small groups (fig. 1). The content of the cytoplasm of some of these reticulum cells indicated erythrophagocytosis. The plasma cells and the reticulum cells were present in the largest numbers. There were also stem cells, normoblasts, some monocytes and a few lymphocytes. No myelopoietic cells were present except some disintegrating myelocytes. The red blood cells were of normal size and shape; megakaryocytes were present in normal numbers.

The blood smears revealed Türk cells that were greatly similar to the plasma cells of marrow. They were round, and their cytoplasm was more basophilic than that of the plasma cells. The nucleus, however, showed the typical cartwheel structure and a paranuclear lighter-stained zone (fig. 2).

At the time of admission the patient had gingivitis and stomatitis. The gingiva was swollen throughout, red, with a velvety, glossy appearance. It might be compared to intestinal mucous membrane. There were necrotic areas of several gingival papillae in the lower as well as the upper jaw (fig. 3). The tissues of the palate showed extensive ulceration and necrosis, especially in the region of the incisors (fig. 4). The margin of the ulceration was grayish, while in the center dark areas of necrotic tissues were seen, impregnated with blood.

The patient complained of severe pain in the entire oral cavity and could swallow only with difficulty. The biopsy specimen was taken from the lower jaw, between the first and the second bicuspid on the left side. When sectioned (fig. 5) it revealed extensive necrosis of the gingiva, extending through the epithelium into the connective tissue. The lesion was sharply limited toward the vital tissues. This was typical coagulation necrosis with the gross outlines of tissues still present. Some remnants of epithelium could still be seen. Bacteria were scarce. Below the necrotic area there was a narrow zone of cellular accumulation.

The epithelial surface showed no keratinization. The cells were somewhat flattened, but neither keratosis nor parakeratosis was present. In the deeper layers of the epithelium edema was manifest. The epithelial cells were separated from each other by wide spaces. The edema was most extensive in the germinative layer. The subepithelial connective tissue was very edematous, showing only a few fibroblasts, blood vessels and wandering cells. Some of the capillaries of this area were empty and contained only few lymphocytes and monocytes. In the entire specimen only one polymorphonuclear leukocyte could be observed, in a blood vessel. The loose edematous tissue contained lymphocytes, monocytes and macrophages.

The borderline between the necrotic and the living tissue is of special interest. The cellular elements in this area were mainly plasma cells and macrophages. Polymorphonuclear leukocytes were absent. Many of the plasma cells and macrophages showed signs of disintegration in this zone. Lymphocytes were scarce.

At some distance from the necrotic area but still close behind the zone of cell accumulation (fig. 6) the cells were in better condition, necrosis being much less pronounced. Plasma cells and macrophages dominated the field; there were only few lymphocytes.

A striking feature of this specimen was the plasma cells. In several regions there were plasma cells with two nuclei, not only singly but in groups of two and more (fig. 7). Some of the plasma cells were small; others, considerably enlarged, showing extensive anisocytosis. Several trinucleated plasma cells of giant size

EXPLANATION OF FIGURES 1 TO 5

Fig. 1.—Sternal marrow; × 958. Mononuclear and binuclear plasma cells and reticulum cells. Plasma cells show anisocytosis. Trinucleated plasma cell; × 1,917.

Fig. 2.—Blood smear showing a Türk cell; × 2,396.

Fig. 3.—Ulceronecrotic lesion on the gingiva.

Fig. 4.—Ulceronecrotic lesion on the palate.

Fig. 5.—General view of a biopsy specimen of the gingiva; × 43. Note the extensive necrosis and the narrow zone of infiltration bordering the necrotic area.

were observed (fig. 8). There were mitotic figures in groups of plasma cells and also in cells within the edematous, loose subepithelial connective tissue. The size of the mitotic cells would indicate that they were plasma cells and macrophages.

In some capillaries a larger number of nongranular mononuclear cells could be seen; these were mainly lymphocytes and monocytes. In some instances these cells migrated from the capillaries into the surrounding connective tissue. The endothelial lining of the capillaries revealed signs of activity. The endothelial cells were more numerous and larger than normal, i. e., swollen.

COMMENT

The observations described are focused on gingivitis and necrotic ulcer.

The velvety quality, the translucency and the red color of the swollen gingiva are due to changes of the epithelium and the subepithelial connective tissue, namely, lack of keratinization in the superficial layers of the epithelium, edema of the deep layers of the epithelium, and edema and hyperemia of the subepithelial connective tissue.

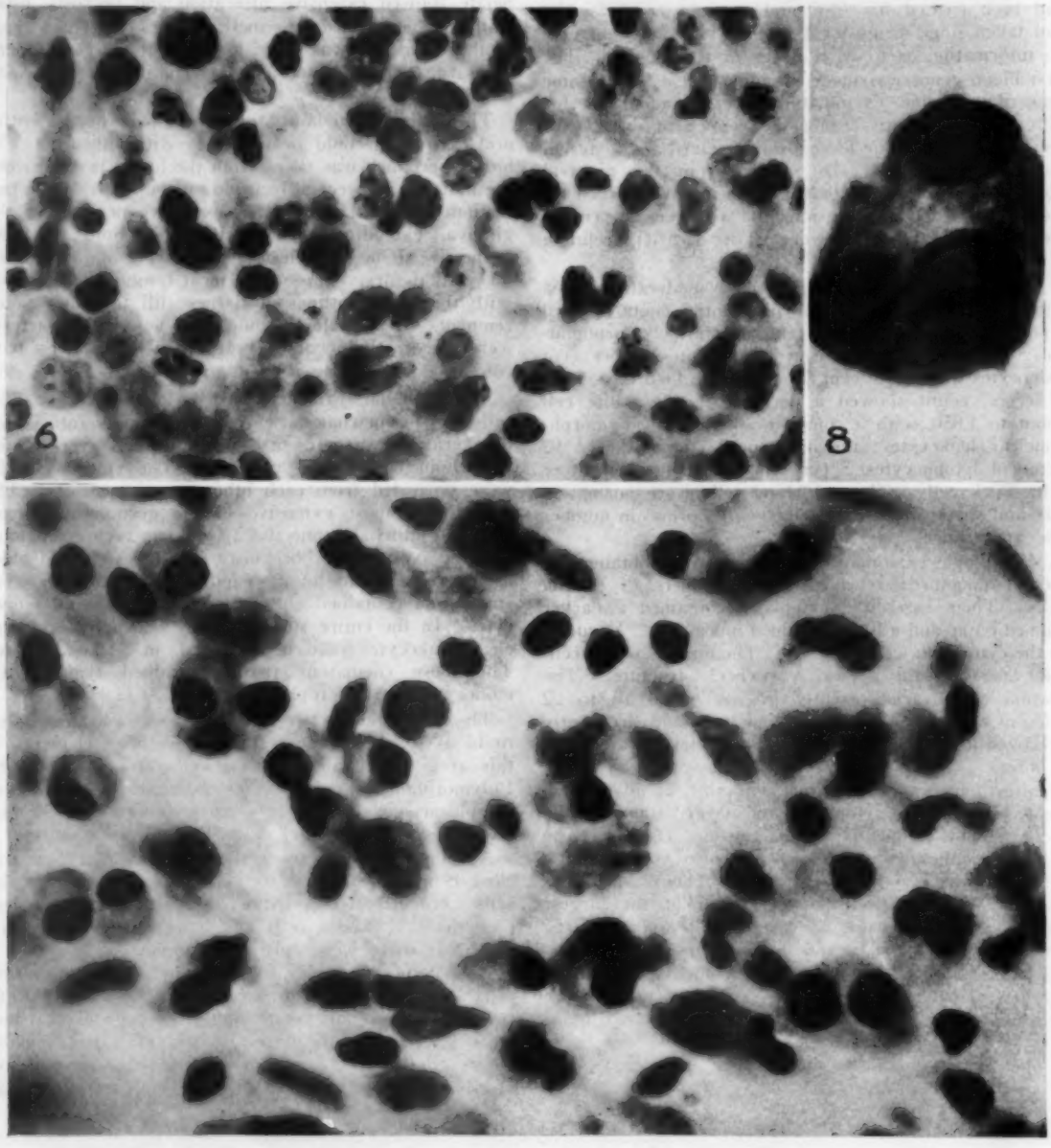

Fig. 6.—Tissue close to the necrotic area in the gingiva; × 1,150. The cellular accumulation consists mainly of plasma cells and macrophages. Only few lymphocytes are present.

Fig. 7.—Gingiva showing several binucleated plasma cells in a group; × 1,342. A few lymphocytes, macrophages and mononucleated plasma cells are present.

Fig. 8.—Trinucleated plasma cell in the gingiva; × 2,300.

The necrotic ulcer reveals necrosis, lack of polymorphonuclear leukocytes, edema and infiltrating plasma cells and macrophages. The first three features are generally accepted characteristics of the necrotic lesion in agranulocytosis; they usually appear following the decrease in the neutrophil polymorphonuclear leukocytes in the blood. The closer mechanism by which they are brought about is entirely unknown.

The changes in the gingival connective tissue were characterized by a decrease in the numbers of certain cells and by an increase in those of others. The cells which decreased in number were those of vascular origin. Not only were the polymorphonuclear leukocytes practically lacking, but the lymphocytes and the monocytes were negligible in number. From capillaries, crowded with large cells, only few lymphocytes and monocytes migrated into the tissues. Among the fixed tissue cells the number of fibroblasts was reduced.

Present in increased numbers were plasma cells and macrophages. The plasma cells were slightly increased in number at the zone of infiltration; they were still more numerous somewhat farther from the area of necrosis. Changes in the quality of the cells also had taken place: Binucleated cells in large numbers, frequently in groups, and trinucleated cells were likewise present. Some binucleated plasma cells and very rarely a trinucleated cell are observed in cases of common gingivitis. In the described case there was an apparent discrepancy between the moderate hyperplasia of the mononucleated and the relatively large number of multinucleated plasma cells.

The macrophages were likewise increased in number. Their cytoplasm and their nucleus were enlarged, and mitotic figures could be seen.

Altogether, it is emphaized that in reaction to the necrosis the gingiva even in the absence of polymorphonuclear leukocytes exhibited proliferative changes, such as proliferation of plasma cells, macrophages and capillary endothelial cells.

In the present case the changes in the marrow showed microscopically certain similarities to the gingival changes. In the marrow the leukocyte-forming cells were lacking. Present in increased numbers were plasma cells, many of which were binucleated and some trinucleated. Plasma cells are normal inhabitants of the marrow, although to a small extent (0.2 to 1.0 per cent). In the present case they far outnumbered the other cells. The binucleated and trinucleated forms appeared numerously and in a shape similar to that seen in the gingiva. Also present in increased numbers were reticulum cells showing erythrophagocytosis.

The type of marrow seen in different cases of agranulocytosis is not uniform. The described type is one of the most frequent and has previously been designated as "aplastic" or "empty" marrow. However, some reports refer to increased numbers of stem cells or plasma cells in such marrow patterns (Leys [16]; Rohr [17]). It is to the credit of Darling, Parker and Jackson [18] that emphasis was placed on the fact that this seemingly "aplastic" marrow is actually hyperplastic with respect to plasma cells, stem cells and reticulum cells, which show more or less marked proliferation.

There is, undoubtedly, a striking similarity in the behavior of the plasma cells and the reticular elements between the gingiva and the marrow. In view of this similarity it is questionable whether these changes are purely local in character, confined to the inflammatory lesion of the gingiva and to the marrow. If they are of a more general character, a similar tissue reaction may be expected of other organs, wherever the plasma cells or the much more widely distributed reticulum cells are normally present. Lacking any autopsy report, we searched for observations on this probability in the literature. There are indications that in some cases plasma cells were present in more or less increased numbers in the lymph glands, the spleen, the peribronchial region of the lung (Plum [13]) and around necrotic lesions of the gastrointestinal tract (Lichtenstein [2]; Plum [13]). Rotter [12] emphasized the hyperplasia and the hypertrophy of the reticuloendothelial cells of the spleen, the lymph nodes and the liver in each of his 6 cases. Similar changes of the Kupffer cells of the liver were observed by Koch,[19] Hallermann,[20] Oppikofer [21] and Plum [13]; whereas Lichtenstein [2] saw no change in the Kupffer cells. The reticulum cells of the lymph nodes and the spleen showed such changes (Dahlen and Wahlgren [22]; Piette [23]; Plum [13]). The histologic observations of Petri [14] are of interest: At the examination of necrotic ulcera-

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23. Piette, E. C.: J. A. M. A. **84**:1415, 1925.

tions of the gastrointestinal tract she noted the same large "lymphoid-like" cells as in the marrow.

It is worth while to emphasize these observations with a purpose to stimulate systematic histologic examinations on extensive and well selected material, including that from patients with different types of agranulocytosis, with different gingival lesions and marrow structures (i. e., "maturation arrest" with myeloid hyperplasia). The impression was gathered that the changes observed in the gingiva and the marrow were not merely accidental or superficial. They indicate, moreover, that, in the course of acute agranulocytosis, when the white cell formation is depressed, conditions are created which favor stimulation of plasma cells and reticulum cells. We wish to point out the possibility that the stimulation of certain cells may not be confined to the marrow and the local necrotic lesion of the gingiva but may represent a reaction on a systemic scale. It may be possible that such observations will ultimately result in an improved classification of cases of agranulocytosis.

SUMMARY

In a case of acute agranulocytosis with ulceronecrotic gingivitis the most characteristic features were lack of keratinization of the epithelium and edema of the deeper epithelial layers, also edema and hyperemia of the subepithelial connective tissue. The necrotic area was surrounded by a narrow zone of infiltration consisting of plasma cells, macrophages and a few lymphocytes. Polymorphonuclear leukocytes were absent. Many binucleated and some trinucleated plasma cells were noted. Mitoses were present. The capillary endothelial cells were swollen. Migration from the capillaries was reduced to a few lymphocytes and monocytes. The tissue changes around the lesion were moderately proliferative.

The sternal marrow lacked myelopoietic cells but showed increased numbers of phagocytic reticulum cells and plasma cells, with many binucleated and some trinucleated forms, similar to those observed in the gingiva.

The question is raised whether the plasmocytic and the reticuloendothelial proliferation in the marrow as well as in other tissues are parts of a systemic reaction.

AORTIC ABNORMALITIES IN DOGS USED FOR EXPERIMENTAL PURPOSES

W. C. HUEPER, M.D.
NEW YORK

Mainly rabbits have been used in past decades for studies on experimental arteriosclerosis and atheromatosis, and a fair amount of information has therefore become available on the occurrence of the various types of so-called spontaneous arterial lesions in this species.[1] The increasingly frequent use of dogs for such purposes in recent years [2] makes it desirable that adequate data on the occurrence, the frequency, the types and the distribution of "spontaneous" arterial lesions in dogs be collected, as such information is essential for the reliable interpretation of experimental observations on canine arteriosclerosis.

It is unfortunate that the mass of the existing data on this subject deals with dogs of a relatively advanced age, i. e., animals which are used comparatively rarely for experimental purposes and which for this reason are of little value when experimental results [3] are being analyzed. The histologic examination of the aortas of 50 mongrel dogs was undertaken in an attempt to provide information on arteriosclerosis occurring in the dogs ordinarily used in experiments.

EXPERIMENTAL PROCEDURE

Aortas were obtained from 50 mongrel dogs which had been killed after being subjected to acute experimentation carried out with the animals under pentobarbital sodium anesthesia and involving in most instances the testing of various vasoactive drugs. The experiments lasted from three to eight hours and were terminated by an intravenous injection of ether. The

Age Distribution of One Hundred and Seventy-Four Mongrel Dogs

	1 to 1.5	2 to 2.5	3 to 3.5	4 to 4.5	5 to 5.5	6 to 6.5	7 to 7.5	8 to 8.5
Years.....								
Number.....	46	48	40	21	10	4	1	3
Per cent....	26.4	27.6	23.5	12.1	5.7	2.3	0.6	1.7

From Warner Institute for Therapeutic Research.

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aorta was dissected out in its entire length, leaving a small portion of the cardiac interventricular septum and the first parts of all the branches attached to the main vessel. This was then cut open lengthwise and rolled up. In this form it was carried through the usual histologic technical procedures of dehydration and infiltration. Sections were cut from the paraffin blocks in such a way that they represented longitudinal sections through the entire aorta. The sections were stained with hematoxylin-eosin, with Hart's modification of Weigert's elastic tissue stain and with Van Gieson's stain for connective tissue.

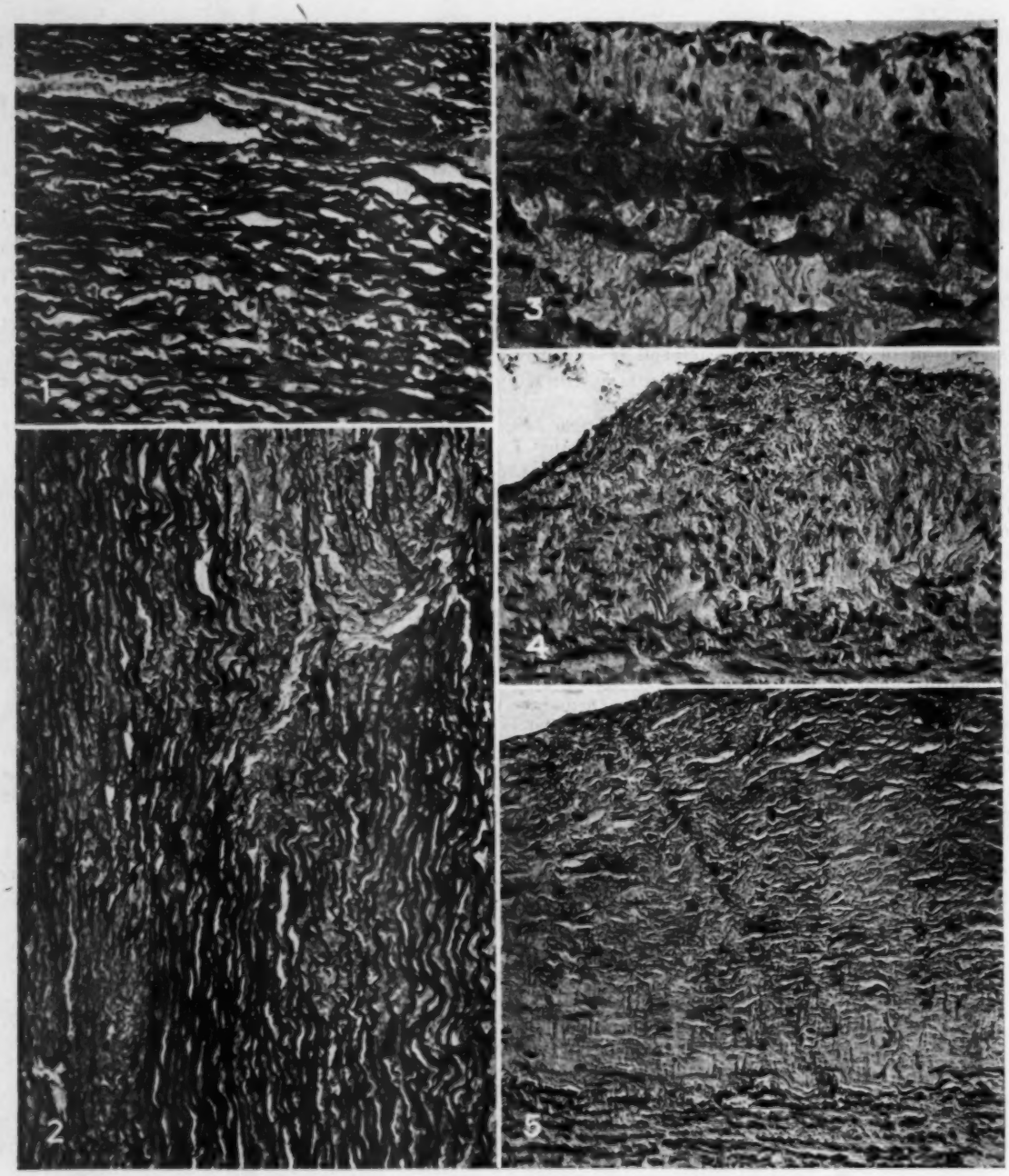

Fig. 1.—Crowding and fragmentation of elastic fibrils in a fibrohyaline area of the outer part of the media in the region of the aortic arch.

Fig. 2.—Perivascular focal interruptions of the elastic membranes of the media in the ascending portion of the aorta.

Fig. 3.—Edematous intimal thickening covering an edematous media in the ascending portion of the aorta.

Fig. 4.—Cushion-like fibrous thickening in the abdominal portion of the aorta.

Fig. 5.—Large fibrohyaline thickening of the lower abdominal part of the aorta.

The ages of 5 of the 50 dogs were known. One was over 8 years, a second 5 years, a third 3 years and the fourth and fifth 1.5 years old. Inasmuch as it seemed to be important to ascertain some information concerning the approximate ages of the rest of the dogs included in this series, the ages of 174 mongrel dogs used later on in the Institute were estimated from the condition of their teeth. The age distribution shown in the table was obtained.

Ninety per cent of the dogs studied were thus in the age range of 1 to 4 years, when "spontaneous" arteriosclerosis is said to be absent in dogs.[4] A similar age distribution presumably prevailed among the animals whose aortas were investigated.

OBSERVATIONS

The histologic examination showed that the inner third of the media of the ascending portion of the aorta and often also of the proximal part of the arch was mildly, moderately or severely edematous in most dogs. The muscle bundles were separated from each other by an irregular and loose felt of fine fibrils or stringy matter staining red with Weigert's connective tissue stain. The elastic membranes in this region were usually fragmented and deranged with the exception of the innermost parts where, as a rule, a dense felt of fine elastic fibrils was present, replacing there an internal elastic membrane. In the descending portions of the aorta a well developed internal elastic membrane was seen. The elastic tissue in the media was well formed, and the fibrils here were rather thick, particularly in the outer part of the media. Wherever these structures joined those of the branches a relatively sudden change in vascular structure occurred. The elastic tissue shifted almost entirely into the outer part of the media, where several thick membranes formed an external elastic coat which surrounded the inner parts of the muscular media containing scanty and delicate elastic fibrils. The muscular tissue in the branches was arranged in definite bundles, which contrasted with the homogeneous muscular coat of the aortic media.

In 6 of the 50 dogs a fibrohyaline scar was found in the outer part of the media approximately 3 to 5 cm. distal from the aortic base. The cicatricial tissue contained usually a moderate number of capillaries and occasionally a few lymphocytes. Collagenous material predominated in such lesions and surrounded fragmented, interrupted, straightened and partly condensed, partly atrophic elastic fibrils (fig. 1). The location of this lesion in the region of the arch corresponded to that of the ligamentum arteriosum. In a moderate number of aortas the presence of circumscribed elastic tissue defects apparently located around or near vasa vasorum was noticed in the media (fig. 2). These interruptions in the elastic membranes appeared in the specially stained sections as "blanched" areas. They affected particularly the central and outer portions of the media. It may be finally mentioned that in 2 dogs there was seen at the distal rim of the aortic bulb large cartilaginous foci surrounded by hyaline tissue forming nodes which projected from the intimal-medial border zone into the vascular lumen.

In addition to these structural variations of nonarteriosclerotic and in part physiologic or congenital nature, the following lesions of doubtful or definite arteriosclerotic significance were observed. Small loose edematous intimal thickenings were seen in the ascending portion of the aorta in 3 dogs (fig. 3). They contained a stringy material staining red with Van Gieson's method and occasionally a few monocytes. A local crowding of endothelial cells in such areas was present in 2 of these dogs. In 2 additional dogs small fibrous intimal thickenings were found in the same location close to the base of the aorta. In one of the two lesions numerous muscular elements were embedded in an intertwining collagenous matrix. A network of delicate elastic fibrils was present in the intimal cushions in both dogs. A small hyaline intimal thickening was seen in the thoracic portion of the aorta of a sixth dog, and several large fibroblastic or fibrohyaline cushions were observed in the abdominal portion of the aorta of a seventh dog (figs. 4 and 5).

A small area of fragmentation and calcification of the internal elastic membrane was noted in the ascending portion of the aorta of an eighth dog (fig. 6), while a ninth dog exhibited in the media of the ascending portion of the aorta several small scattered areas in which the muscle cells had a homogeneous, pink-stained cytoplasm and were loosely packed, indicating localized muscular degeneration and atrophy (fig. 7). The cellular nuclei were distinctly diminished in number.

The proximal parts of the numerous aortic branches, especially the common iliac arteries, which were often included in the sections, were normal with the following exception. The medial sacral artery of the oldest dog of this series revealed a considerably and concentrically thickened fibrohyaline intima and a calcified internal elastic membrane causing a distinct narrowing of the vascular lumen (fig. 8). The thickening was free from elastic fibrils.

4. (*a*) Strauch, C.: Beitr. z. path. Anat. u. z. allg. Path. **61**: 532, 1916. (*b*) Krause.[3c]

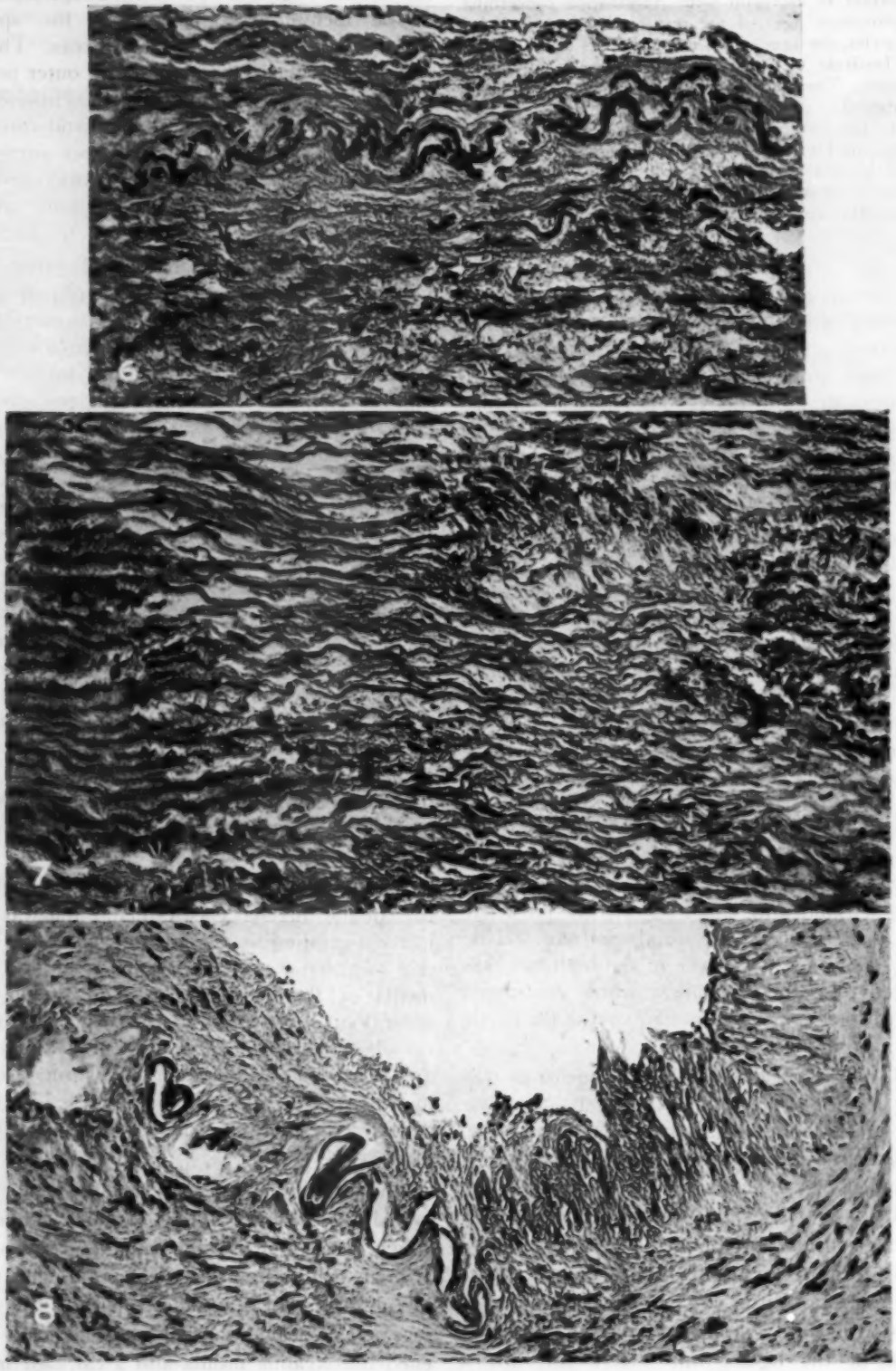

Fig. 6.—Calcification and fragmentation of the internal elastic membrane of the ascending portion of the aorta.
Fig. 7.—Circumscribed degeneration of the media of the aorta.
Fig. 8.—Concentric fibrous intimal thickening with calcification of the internal elastic membrane of the medial sacral artery.

COMMENT

Marked edema of the inner part of the media of the ascending portion of the aorta, present in the majority of the dogs, was reported by Zinserling [3k] as a normal condition of the canine aorta. It has been looked on as an agonal phenomenon related to prolonged circulatory failure preceding the final arrest of circulation. This concept was supported by Wiesel [5] and by Segre and Kellner,[6] who made similar observations in the arteries of man and animals. Segre and Kellner considered the albuminous matter filling the interstices between the widely separated muscle bundles as the product of agonal contraction of the muscle cells by which cellular fluid is expressed into the intercellular spaces. This interpretation, however, is in disagreement with that placed on this matter by Sternberg [7] and Albrecht.[8] These investigators regarded the edematous imbibition of the arterial media as a postmortem change. Wiesel,[5] on the other hand, thought that it accompanied exclusively acute or chronic cardiac and infectious diseases associated with circulatory failure. The loose edematous structure of the ascending portion of the aorta of the dog is not a consistent phenomenon, as it was absent in some 5 aortas.

The presence of cartilaginous tissue in the distal rim of the aortic bulb observed in 2 dogs is probably related to the occurrence of similar cartilaginous or, occasionally also, osseous plates in the aortic rim in various animals, including dogs (Spiegel [3g]; Hueper [2c]), and does not seem to represent a part of an arteriosclerotic process.

The occurrence of circumscribed defects in the elastic tissue such as those observed in some of the aortas has been previously recorded by Krause and Strauch, who found such tears in the elastic membranes of even young dogs.[4]

Of the edematous or fibrosing intimal thickenings present in the ascending portion of the aorta in 5 dogs, those of edematous type were obviously of relatively acute and reversible nature and all of them were comparatively small and circumscribed and thus possibly early arteriosclerotic developments. Only the fibrohyaline intimal cushions found in the abdominal portion of the aorta of 1 dog can be considered definite and advanced arteriosclerotic lesions, which were associated with granular calcification of the fragmented and swollen internal elastic membrane present underneath some of these reactions. Thus in only 1 dog of a total of 50 was well developed, though localized, arteriosclerosis of the aorta demonstrable. Inasmuch as the 2 dogs, 8 years and 5 years old, respectively, showed merely small intimal thickenings of the ascending portions of the aorta, it can be assumed that the animal with arteriosclerosis must have been either especially well advanced in age, because the great majority of the dogs were doubtlessly not more than 4 years old, or represents an exceptional occurrence of arteriosclerosis in a young dog.

These observations demonstrate that young dogs can be used for the experimental production of arteriosclerosis without fear of any appreciable and significant spontaneous arteriosclerotic lesions being encountered. They do not lend support to the claim that the distemper usually developing in young dogs has any etiologic role in the development of such changes as contended by Köllisch [3b] and denied by Strauch.[4a] The anatomic type of lesions observed is that noted after severe and prolonged fluctuations in the tonus of vessels or in intravascular hydrostatic pressure. It is purely speculative, however, whether or not the marked changes in blood pressure readily elicited in dogs by psychic stimuli have any causal relation to the sclerosing arterial manifestations frequently seen in old dogs. Fox stated that domesticated dogs show arteriosclerosis after the fifth year of life as pebbly granular thickenings in the lower thoracic and abdominal portions of the aorta, consisting of fibrous intimal hyperplasia rarely breaking through the internal elastic membrane, with occasional calcifications of the media underneath. He noted that aortic calcifications occur in domestic dogs rarely and are then usually found in the beginning portion of the aorta.

Köllisch,[3b] who studied 50 working dogs, 2 to 7 years old, and 50 luxury dogs, 8 to 20 years old, recorded arteriosclerosis in 10 of the working dogs and in 3 of the luxury dogs, or in 23 per cent of the total number. The lesions of 7 of these dogs consisted of partly rough-surfaced, partly smooth-surfaced round or irregular intimal thickenings, while in the other 16 dogs round projecting intimal cushions existed. In 2 instances the entire aorta was calcified. The intimal thickenings were of the fibrous type, containing fat only rarely. Medial lesions exhibited local fibrosis and occasionally calcification, with fibrillar cartilage sometimes surrounding the calcified foci. Strauch [4a] made a thorough study of the various large and medium-sized arteries of 56 dogs, 47 of them aged 1 to 5, and 9 of them aged 5 to 8.

5. Wiesel, J.: Wien. Arch. f. inn. Med. **1**: 197, 1920.
6. Segre, R., and Kellner, E.: Centralbl. f. allg. Path. u. path. Anat. **32**: 561, 1921-1922.
7. Sternberg, C.: Wien. klin. Wchnschr. **31**: 297 and 310, 1921.
8. Albrecht, H., cited by Segre and Kellner.[6]

He examined the following arteries: the aorta, the innominate, subclavian, common and external carotid, celiac, superior mesenteric, phrenic, renal, internal spermatic, femoral, hypogastric, medial sacral, coronary, splenic, hepatic and pulmonary arteries and in some cases also the cerebral, brachial and saphenous arteries. In only 1 of the 47 young dogs early arteriosclerotic changes were seen (2.2 per cent). Cushion or ridgelike rough intimal fibrous thickenings of the aorta, on the other hand, were noted in 6 of the 9 old dogs (67 per cent). The lesions were usually located distal from the entrances of the renal arteries. Fat was rare and scanty in these foci. The observations as to the comparative frequency of arteriosclerosis in old dogs made by Strauch [4a] are supported by the findings of Zinserling [3k] in 26 old dogs (8 to 28 years of age). Every one of these old dogs had fibrous intimal thickenings of the aorta; all except 3 had lipoid deposits in the aorta, and all of them had such lesions in the splenic artery. The fat was usually found in the form of fine droplets or as a diffuse imbibition in the ground substance of the media of the ascending part of the aorta, often arranged along the elastic membranes. Macrophages with fat were occasionally seen. The type of fatty infiltration of the canine aorta thus differs distinctly from that found in human atherosclerosis. Extensive medial calcinosis and fibrosis, occasionally associated with the appearance of cartilaginous tissue, was observed by Zinserling [3k] in the aortas of old dogs (11 to 16 years). Krause,[3e] on the other hand, missed any medial calcification in even the oldest dog studied by him, and noted medial calcifications of the aorta in only 2 dogs with generalized arterial calcifications, which he attributed to a disturbance of the calcium metabolism. Fibrous intimal thickenings of the aorta are, according to him, commonly present in dogs more than 5 years old.

Special mention may be made of the circular fibrous intimal thickening of the medial sacral artery of 1 dog. In view of the fact that this was practically the only aortic branch which revealed any sclerotic change and that the sclerosis was of concentric type involving the entire circumference of the vessel, consideration must be given to the possibility that changes in the normal hydrostatic pressure may have been responsible for this lesion. It is the medial sacral artery which supplies blood to the tail of the dog. An amputation of this organ would result in a temporary marked increase of intravascular hydrostatic pressure, which conceivably may elicit the reported type of arterial change. This explanation, however, must remain speculative, as no data are available on the question whether or not this particular dog had an amputated tail.

SUMMARY

Arteriosclerosis of the aorta is exceptional in dogs before the age of 5. The arterial lesions met with in dogs are predominantly of the sclerosing type. The highly edematous state of the inner part of the media of the ascending portion of the aorta frequently seen in dogs is either a normal anatomic condition or an agonal phenomenon resulting from circulatory disturbances.

COMBINED EFFECTS OF AN ESTROGEN AND AN ANTERIOR HYPOPHYSIAL EXTRACT ON THE SKELETON OF THE GROWING MOUSE

MARTIN SILBERBERG, M.D., AND RUTH SILBERBERG, M.D.
ST. LOUIS

Estrogen and a hormone produced by the anterior lobe of the hypophysis accelerate skeletal aging in growing animals.[1] However, the two hormones accomplish this effect in different ways: The anterior hypophysial hormone stimulates growth and hastens epiphysiodiaphysial union by inducing premature regression and resorption of the epiphysial cartilage; estrogen, on the other hand, inhibits growth and resorption, thus delaying epiphysiodiaphysial union. In view of these contrasting mechanisms we thought it of interest to investigate the combined effects of these two hormones on skeletal development and aging.

MATERIAL AND METHODS

Thirty-two virgin female mice 5 to 6 weeks old were used. Of these, six pairs of D mice received subcutaneous injections of 100 rat units of alpha estradiol benzoate in sesame oil[2] once weekly and intraperitoneal injections of 0.1 cc. of an extract of the anterior lobe of the bovine hypophysis five times weekly for one week, one, three, five, ten and sixteen months, respectively; seven pairs of C$_3$H mice were treated correspondingly for four, six, seven, eight, nine, ten and eleven months; three pairs of A mice received the same treatment for one week, two weeks and one month. The anterior hypophysial extract was prepared according to the method of Loeb and Basset.[3] Untreated mice and animals which had been treated only with the estrogen or with the anterior hypophysial extract and which had been used in former experiments, served as controls. The mice were kept on a standard diet of Purina dog chow with water available at all times. At the end of the experimental period they were killed with chloroform; the lower part of a femur and the upper part of a tibia were taken out as a whole and prepared for histologic examination.[4]

HISTOLOGIC EXAMINATION

The following description is based on the observations of the tibia.

Epiphysial Disk.—After one week of the combined treatment the epiphysial cartilage proliferated by way of mitosis and underwent marked hypertrophy. However, these processes were less intensified than after injections of the anterior hypophysial extract alone. The individual cartilage cell row was composed of eight columnar and one or two hypertrophic cells. The corresponding figures for untreated animals were seven or eight columnar and two or three hypertrophic cells. For mice receiving the anterior hypophysial extract alone the figures were seven or eight columnar and one or two hypertrophic cells. In animals given the estrogen only, there were but five or six columnar and one or two hypertrophic cells in the individual cartilage row; the mitotic proliferation and the conversion of columnar into hypertrophic cartilage cells were markedly decreased. On the whole, after one week's injections of the estrogen and the anterior hypophysial extract the growth zones resembled closely those seen in mice treated with the anterior hypophysial extract alone, but calcification and ossification were more accentuated than in either the latter or in normal animals.

If the two hormonal preparations were allowed to act for two weeks, the epiphysial plate was narrower than ordinarily. Mitotic proliferation and hypertrophy of the columnar cartilage were still marked. There were five or six columnar and one or two hypertrophic cells instead of seven columnar and two or three hypertrophic cells as is normal. In animals given the anterior hypophysial extract only, six or seven columnar and two or three hypertrophic cells were counted in the single cell row; in mice receiving the estrogen alone the corresponding figures were five or six columnar and one or two hypertrophic cells. Therefore, under the combined influence of both hormones the width of the epiphysial plate was comparable to that found after injections of the estrogen alone; however, both proliferation and hypertrophy of the epiphysial cartilage were less decreased than after administration of the estrogen alone.

After one month of the combined treatment the narrowed growth zones were densely calcified. In

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From the Laboratory of Research Pathology, Washington University School of Medicine, the Snodgras Laboratory, City Hospital, and the Laboratory of the Jewish Hospital.

1. Silberberg, M., and Silberberg, R.: Arch. Path. **36**:512, 1943.

2. The alpha estradiol benzoate in sesame oil was supplied by Dr. Erwin Schwenk, of the Schering Corporation.

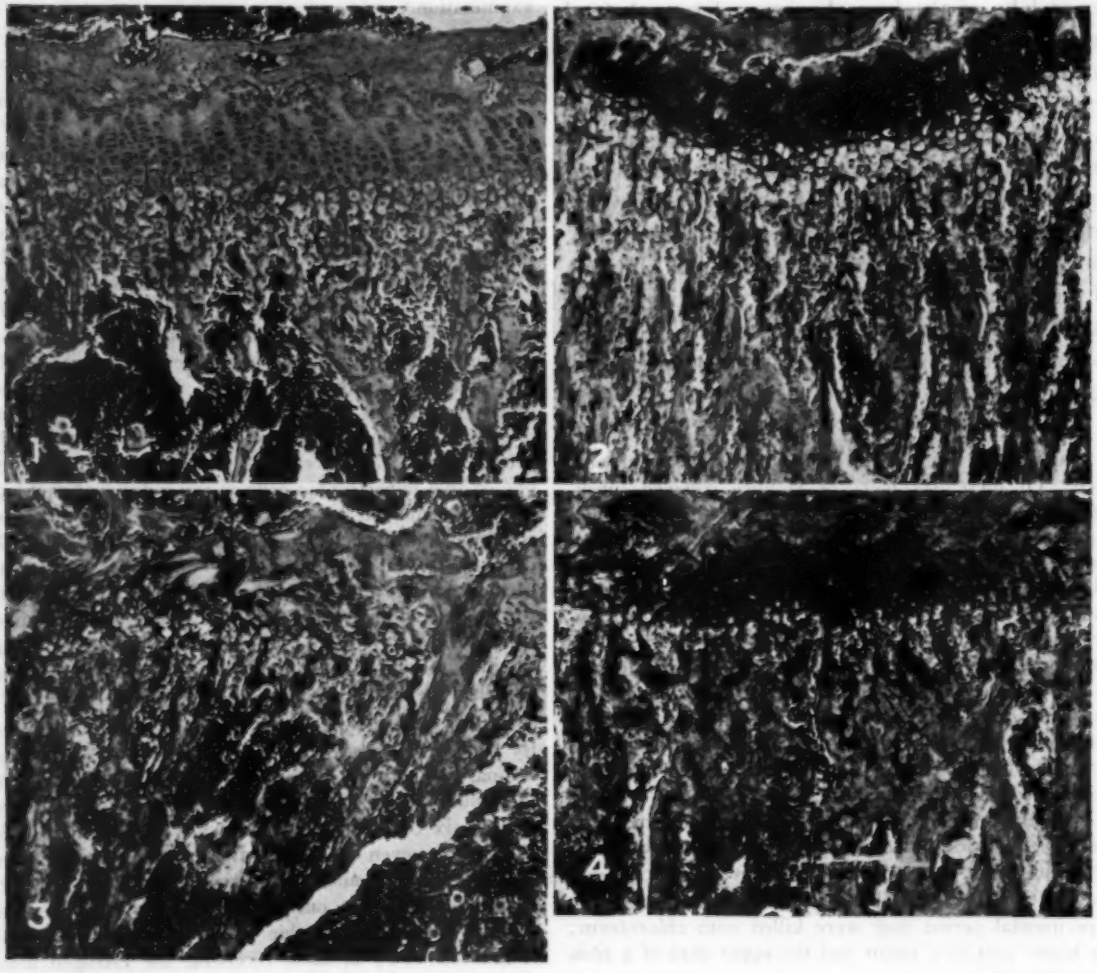
3. Loeb, L., and Basset, R. B.: Proc. Soc. Exper. Biol. & Med. **26**:860, 1929.

4. (*a*) Silberberg, M.: Proc. Soc. Exper. Biol. & Med. **32**:1423, 1935. (*b*) Silberberg, M., and Silberberg, R.: Am. J. Anat. **68**:69, 1941.

areas where calcification was somewhat lighter there were four or five columnar cartilage cells and one hypertrophic cell in a single row. Both cell types were smaller than usual; mitoses in the cartilage were scarce; calcification was more prominent than after administration of the anterior hypophysial extract alone. The growth zone appeared at this stage not unlike that seen after injections of the estrogen alone; in animals treated only with the anterior hypophysial extract bony plugs had replaced the destroyed cartilage cell rows and were already being resorbed by advancing marrow (figs. 1 to 4).

zones which showed resorption by capillaries advancing from the marrow.

After four or five months of combined treatment the resorption was even more accentuated: In mice of strain C_3H the epiphysial plate had to a large extent been replaced by a fibro-osteoid tissue originating in the metaphysis. In nontreated animals, thick bony plugs were present in the inactive cartilage, but there were no perforations of the growth zones. Under the influence of the anterior hypophysial extract alone, perforations of the epiphysial disks appeared at this stage but without the formation of fibro-osteoid tissue. In



Each of the sections shown was made through the epiphysial disk of the upper part of a tibia of a virgin mouse of strain A 9 weeks old.

Fig. 1.—Section from an untreated animal; × 100. The growth zone shows regular configuration.

Fig. 2.—Section from a mouse given 100 rat units of an estrogen by injection once a week for one month; × 100. The growth zone is narrowed and heavily calcified; interlacing trabecular bone is seen in the metaphysis.

Fig. 3.—Section from a mouse given 0.1 cc. of a bovine anterior hypophysial extract by injection five times weekly for one month; × 100. The epiphysial cartilage is broken down, showing plug formation.

Fig. 4.—Section from a mouse given both the estrogen and the anterior hypophysial extract for one month; × 100. Note the narrowed, densely calcified growth zone and the numerous thick mature trabeculae in the metaphysis.

Administration of both preparations for three months further increased calcification and ossification of the cartilage: Numerous bony plugs traversed the growth

mice receiving only the estrogen the growth zones still consisted of a continuous layer of calcified cartilage; bone deposition in the epiphysial plate was predominant,

whereas resorptive processes were insignificant (figs. 5 to 8).

If both hormonal preparations were given for from six to nine months, the fibro-osteoid tissue was resorbed and replaced by cellular marrow. The wide gaps in the epiphysial plate were even more conspicuous, since untreated mice of strain C$_3$H show little tendency toward perforations of the growth zones. Thus the skeletal age of the epiphysial disk was comparable to that of untreated virgin mice during the second year of life. After administration of the estrogen alone, no such perforations were found; in mice receiving only the anterior hypophysial extract, resorption progressed, still without production of fibro-osteoid tissue.

If the combined treatment was continued further, only scanty remnants of calcified cartilage were left of the epiphysial disk or it was converted into a thin bony scar, both rather uncommon occurrences in old untreated mice. After fourteen months of injections, epiphysiodiaphysial union was not so far advanced as in animals given the anterior hypophysial extract alone; however, resorptive processes were more advanced than in mice receiving only the estrogen (figs. 9 to 12).

Diaphysis.—After one and two weeks of the combined treatment the osetoblasts in the metaphysis and along the bony trabeculae proliferated by way of mitosis. There was more connective tissue in the subepiphysial layer than usual; the spicules were thicker than ordinarily or after treatment with either hormonal preparation alone. There was less vascularization than after injections of the anterior hypophysial extract but more than after administration of the estrogen only. The trabeculae were firmer, shorter and more widely spaced than under the influence of the estrogen.

After one month of the combined treatment a transverse bony plate had been laid down beneath the calcified cartilage, indicating cessation of growth. The metaphysial connective tissue had further increased in density and amount; osteoblastic proliferation showed a marked decline but no standstill as in estrogen-treated animals; the trabeculae were coarser, more numerous and much thicker than during the earlier stages. However, the interlacing bony network, so prominent after injections of estrogen alone, was not found (figs. 1 to 4). The vessels of the shaft were moderately filled; mitotic proliferation of the periosteum and the endosteum was scarce or lacking; the compacta was thicker than usual and contained numerous small osteocytes. In untreated animals osteoblastic proliferation was still marked at this age. After injections of the anterior hypophysial extract, osteoblastic proliferation was stimulated, the shafts contained enlarged capillaries, and the periosteum and the endosteum were loosened. In estrogen-treated animals, on the other hand, the vascular canals were narrowed and less numerous than ordinarily; a dense connective tissue had developed in close approximation to the thickened shafts, and mitotic proliferation in this tissue was scarce, if present at all.

After three months of treatment the transverse bony plate underneath the calcified cartilage was irregular and thinned out. It was connected with the interlacing spicules now present throughout the metaphysis and in the corners between the metaphysial plate and the shaft. This network was at the same time being resorbed by a fibro-osteoid tissue which also penetrated into the remnants of the epiphysial disk (figs. 5 to 8). Between the spicules and the fibro-osteoid tissue some marrow was found. Farther distally, the hemopoietic marrow was more prominent, but it still contained undissolved irregular trabeculae. This or a similar histologic pattern was never observed in the metaphysis of any untreated mouse or of any receiving only the anterior hypophysial extract. The condition resembled that seen in mice treated with the estrogen for six or more months, that is, twice as long as in the series given the combined treatment.

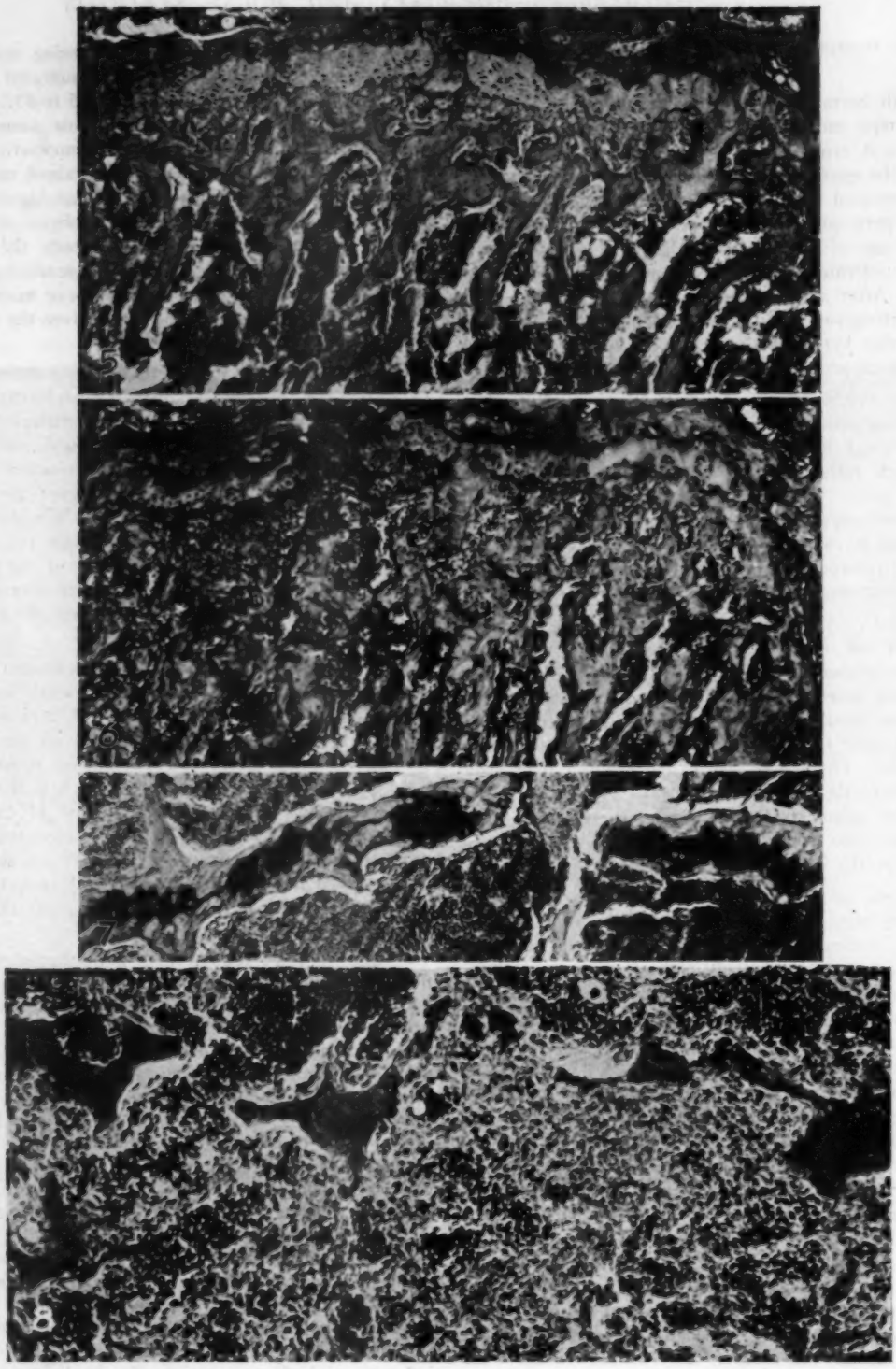
After four, five or six months of the combined treatment the resorptive processes were accentuated. The bony plate underneath the calcified cartilage was corroded from below by marrow; the connective tissue in the metaphysis showed better vascularization and less hyalinization than at the earlier stages; the spicules were thinned out and shortened, and the shafts were likewise thinner. There was less bone present than before and less than after injections of the estrogen alone. However, bony tissue was more abundant than in either untreated animals or mice receiving the anterior hypophysial extract.

If the administration of both the estrogen and the anterior hypophysial extract was continued, the resorptive processes were further intensified, and they were ahead of those found after treatment with the estrogen alone. In mice treated for seven to nine months, there were only traces of a thin bony network in the marrow cavity, and after sixteen months most of the excess bone and the connective tissue had disappeared. There were still scanty remnants of irregular spicules which distinguished this series from untreated animals as well as from those given the anterior hypophysial extract alone (figs. 9 to 12).

Joints.—In mice treated with both the estrogen and the anterior hypophysial extract for from one week to one month the articular cartilage cells underwent slight to moderate hyperplasia and hypertrophy and at the same time some degeneration, changes that were classified as grade I. With increasing duration of the experiment, these alterations did not make much progress. As a rule, the cartilaginous matrix underwent pronounced hyalinization. Only 1 animal showed articular changes of grade II, namely, moderate proliferation and regression of the cartilage. Grade III, that is typical osteoarthritic changes, were not observed in the animals given the combined treatment, whereas such lesions did occur in many untreated old mice.[5] Administration of the estrogen alone decreased the incidence and the severity of these articular changes; conversely, treatment with the anterior hypophysial extract alone hastened their onset and increased their incidence and severity.[6] Under the influence of both preparations the hyalinization of the cartilage caused by the estrogen probably counteracted the liquefying effect of the growth-stimulating factor in the anterior hypophysial extract and thus prevented a breakdown of the articular cartilage.

5. Silberberg, M., and Silberberg, R.: Anat. Rec. **91**:89, 1945.

6. Silberberg, M., and Silberberg, R.: Am. J. Path. **17**:189, 1941.



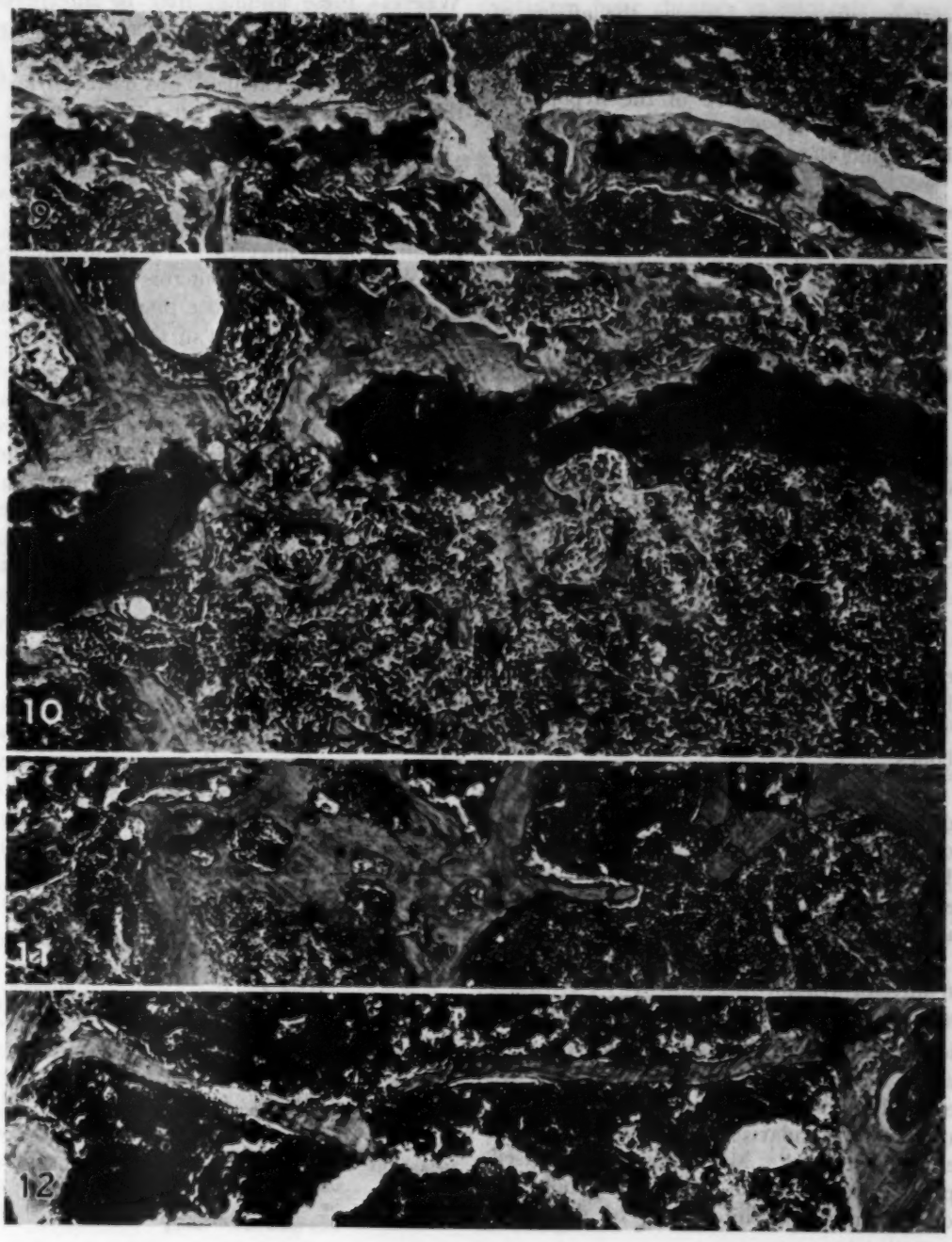
Each of the sections shown was made through the epiphysial disk of the upper part of a tibia of a virgin mouse of strain C$_3$H 6 months old.

Fig. 5.—From an untreated animal; × 100. Note plugs of regressed cartilage in the inactive growth zone.

Fig. 6.—From a mouse which had received 100 rat units of an estrogen by injection once a week for five months; × 100. A dense interlacing trabecular network may be seen in the metaphysis, with scanty remnants of marrow between the spicules.

Fig. 7.—From a mouse which had received 0.1 cc. of a bovine anterior hypophysial extract by injection five times weekly for five months; × 100. The growth zone is represented by a bony plate containing remnants of calcified cartilage. Note the wide communication between the epiphysis and the diaphysis.

Fig. 8.—From a mouse to which both the estrogen and the anterior hypophysial extract had been administered for five months; × 140. In the left upper corner of the growth zone are small amounts of cartilage. Fibro-osteoid tissue has developed in the epiphysis and the diaphysis.



Each of the sections shown was made through the epiphysial disk of the upper part of a tibia of a virgin mouse of strain D 17 months old. × 100.

Fig. 9.—Section from an untreated animal; × 100. Note remnants of calcified cartilage in the growth zone perforated by bone marrow.

Fig. 10.—Section from a mouse given 100 rat units of an estrogen by injection once weekly for sixteen months; × 140. Note remnants of calcified cartilage in the growth zone and formation of fibro-osteoid tissue in the metaphysis.

Fig. 11.—Section from a mouse given 0.1 cc. of a bovine anterior hypophysial extract by injection five times weekly for sixteen months; × 100. There is complete epiphysiodiaphysial union, with wide communications between the epiphysis and the diaphysis.

Fig. 12.—Section from a mouse to which both the estrogen and the anterior hypophysial extract had been administered for sixteen months; × 100. A bony scar has taken the place of the growth zone. The marrow is cellular, and no trabecular bone is present.

COMMENT

A certain antagonism between the effects of anterior hypophysial and estrogenic hormones has been demonstrated in various tissues: An extract of the anterior lobe of the hypophysis loosens the connective tissue [7] and increases the vascularity and the uptake of water by the tissues.[8] Estrogen, on the other hand, promotes the deposition of hyalin in the uterus, the vagina and the adrenal glands,[9] in cartilage and in marrow,[10] and it decreases the water content of the long bones.[11]

TABLE 1.—*Skeletal Changes After One Month of Treatment*

		Anterior Hypophysial Extract	Estrogen	Anterior Hypophysial Extract and Estrogen
Epiphysial cartilage	Growth	Increased	Decreased	Somewhat decreased
	Regression	Increased	Increased	Markedly increased
Metaphysis	Connective tissue	Loosened, with vascularization increased	Hyalinized, with vascularization decreased	Somewhat hyalinized, with vascularization decreased
	Bone	Ossification increased; short trabeculae	Resorption decreased; interlacing trabeculae	Fairly long, mature thick trabeculae

In view of these antagonisms it might be assumed that estrogen and the growth-promoting hormone of the anterior lobe of the hypophysis would each diminish the effect of the other. However, this does not seem to be generally true. The accompanying tables demonstrate in a schematic way skeletal changes caused by injections of (*a*) an anterior hypophysial extract, (*b*) estradiol benzoate in sesame oil and (*c*) both together.

After one month of the combined treatment (table 1), the growth of cartilage was less decreased, and the connective tissue was less hyalinized and better vascularized, than after injections of the estrogen alone. Moreover, the increased resorption caused by the anterior hypophysial extract prevented the interlacing of the bony spicules seen after treatment with the estrogen. Whereas these findings may be interpreted as antagonistic effects, there was also a certain synergism of the two hormones noticeable. The regression of the cartilage was more marked, and the bone was thicker, than after treatment with either alone. The changes in the bone represent a combination effect involving two different mechanisms: The anterior hypophysial extract stimulated osteoblastic bone formation; the simultaneously injected estrogen diminished the osteoblastic activity. But this decrease in active bone formation was more than compensated for by the lag of resorption of the primary spicules.

The findings after six months of treatment are summarized in table 2. The synergistic action of the estrogen and the anterior hypophysial extract is reflected in the marked resorption of the epiphysial plate, which was more advanced than after treatment with either alone. Whereas under the influence of the anterior hypophysial hormone the epiphysial plate was resorbed by marrow, in the series given both preparations it was dissolved by fibro-osteoid tissue. The latter appeared earlier than in animals treated with the estrogen alone. In no instance was this tissue tumorous in character; it disappeared as soon as the excessive bone had been resorbed. This suggests that the fibrous metaplasia of the marrow represents a reaction of the organism to the excess bone and not simply a specific hormonal effect. In normal animals, as well as in those treated with the anterior hypophysial extract, the solution of the trabeculae is accomplished by capillaries or body fluids. The more abundant and the denser the bone, the more inadequate are the normal mechanisms of solution. It is conceivable that the additional resorptive power of connective tissue is needed to restore the normal tissue equilibrium. A direct stimulation of the connective tissue by

TABLE 2.—*Skeletal Changes After Six Months of Treatment*

	Anterior Hypophysial Extract	Estrogen	Anterior Hypophysial Extract and Estrogen
Epiphysial cartilage	Inactive, with marked resorption by marrow	Ossifying, inactive, with little resorption	Marked resorption by connective tissue; fibro-osteoid tissue present
Metaphysis	Hemopoietic marrow present; few thin trabeculae	Much trabecular bone, some interlacing	Fibro-osteoid tissue present
Articular cartilage	Softened, hypertrophic and hyperplastic	Hyalinized	Hyalinized

7. Loeb, L., in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1940, vol. 36, p. 228.

8. Downs, W. G., Jr.: Arch. Path. **12**:37, 1931. Long, C. N. H., in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1942, vol. 4, p. 465. Silberberg and Silberberg.[1]

9. Loeb, L.: The Biological Basis of Individuality, Springfield, Ill., Charles C Thomas, Publisher, 1945.

10. Silberberg, M., and Silberberg, R.: (*a*) Arch. Path. **28**:340, 1939; (*b*) Am. J. Anat. **69**:295, 1941. Landauer, W., and Zondek, B.: Am. J. Path. **20**:179, 1944.

11. Lippman, H. N., and Saunders, J. B. de C. M.: J. Endocrinol. **3**:370, 1944.

the anterior hypophysial hormone may partly account for the early fibrous metaplasia of the marrow.

In a previous investigation [5] we examined the effects of syngenesiotransplants of the anterior lobe of the mouse hypophysis. Not only did these transplants give off hormones acting on the skeleton but they also stimulated the production of estrogen in the transplant-bearing host. The latter was thus exposed to increased amounts of both anterior hypophysial and estrogenic hormones. In these animals the growth of cartilage was inhibited presumably because of the predominance of the estrogen effect. On the other hand, the anterior hypophysial hormone apparently maintained the proliferation of the cartilage longer than ordinarily. Whereas these findings likewise indicated an antagonistic action of the two hormones, others suggested a certain synergism. As in the present series, the regression of the epiphysial cartilage was more intense and more bone was formed than after treatment with either the estrogen or the anterior hypophysial extract alone.

Thus, the skeletal effects of anterior hyophysial and estrogenic hormones are opposed to each other in some respects, but they do not neutralize each other. In the present experiments the estrogen effect on the bone tended to outbalance that of the anterior hypophysial hormone. The following factors may be responsible for this occurrence: 1. The anterior hypophysial extract loses its effectiveness with prolonged administration.[1] 2. There is a gradation in the reaction of various species to hormonal stimulation. The sensitivity of the skeletal tissues to estrogen increases in the following order: guinea pig, rat, mouse; on the other hand, mice respond to anterior hypophysial extract less readily than guinea pigs. The predominance of the estrogen effect in our mice may thus have been due to the greater responsiveness of this species to estrogen than to the anterior hypophysial hormone. 3. The dose of the estrogen given may have been too high in proportion to that of the anterior hypophysial extract. However, it is difficult to obtain consistent bone changes in mice with doses less than 100 rat units weekly. On the other hand, the dose of the anterior hypophysial extract given was fairly high already.

The present observations suggest that estrogen acts on the skeleton directly and not by mediation of the anterior lobe of the hypophysis. If the estrogen effects were the result of an inhibition of the anterior lobe of the hypophysis, they should have been counteracted by the administration of an extract of the anterior lobe of the pituitary gland. Moreover, if the estrogen effects were mediated in some other way by the anterior lobe of the hypophysis, they should be lacking in hypophysectomized animals. However, in pigeons hypophysectomy did not measurably modify the medullary bone formation and the increase of the serum calcium seen under the influence of estrogen.[12] Furthermore, in hypophysectomized mice, estrogen increased the ash content of the long bones, although to a lesser extent than in intact animals.[13]

SUMMARY

In growing mice the skeletal effects of estrogen can be modified by the simultaneous administration of an extract of the anterior lobe of the hypophysis. The two hormones oppose each other in their action on the growth of cartilage, but they cooperate in accelerating the age changes in the latter and in the overproduction of bone, anterior hypophysial hormone by stimulating osteoblastic bone formation and estrogen by promoting hyalinization of the marrow and by inhibiting the resorption of bone. Thus, the two hormones do not neutralize each other but each tends to exert its own effects on the receptor tissue. The skeletal effects of estrogen are direct ones and not mediated by the anterior lobe of the hypophysis.

12. Riddle, O.; Rauch, V. M., and Smith, G. C.: Endocrinology **36**:41, 1945.

13. Gardner, W. U., and Clouet, D. H.: Anat. Rec. **88**:433, 1944.

Case Reports

TULAREMIA

A Report of a Laboratory Infection Fatal on the Fifth Day, with Early Pulmonary Involvement; Autopsy

L. L. Ashburn, M.D., Surgeon, United States Public Health Service
BETHESDA, MD.
AND
Seward E. Miller, M.D., Surgeon, United States Public Health Service
BALTIMORE

Tularemia in man has been well characterized from the standpoint of pathology in various reports based on autopsies in 73 cases. In the great majority of these cases the interval between the onset of the disease and death exceeded twelve days, and we have found only 1 case reported with autopsy in which the duration of the disease was less than eight days (four days seven hours).[1] We wish to report a case with autopsy in which the duration was four days sixteen hours. In this case cough was one of the earliest symptoms, Pasteurella tularensis was present in the sputum sixteen hours after onset, and the only organisms demonstrated in the sections of the pneumonic lung were morphologically consistent with P. tularensis.

REPORT OF A CASE

R. P., a white woman aged 55 years, was admitted to the United States Marine Hospital, Baltimore, complaining of cough, fever, headache, weakness, and pains in bones, muscles and joints. Except for Q fever in 1940, the past medical history was of no interest.

The patient was a technician in a laboratory where tularemia and leptospirosis were under experimental investigation. However, she did not come in intimate contact with tularemic animals and did not handle cultures of P. tularensis.

On Sept. 6, 1944, about 5 p. m., while on her way home from work, the patient felt feverish and shortly afterward a severe headache, cough, nausea and pains in muscles, bones and joints developed, with general malaise. The cough was irritating and dry. She slept poorly that night and had two or three loose bowel movements. In the morning her temperature was 103 F., and the symptoms were more severe, particularly the cough. Blood and sputum were obtained for culture and animal inoculation, and she was taken to the hospital at 4 p. m., September 7. On arrival her temperature was 104.4 F., with a pulse rate of 120.

Examination on admission showed moderate obesity, flushing of the face, moist skin, slightly inflamed conjunctivas with increased lacrimation, a somewhat congested nasal mucous membrane with little seromucoid discharge, a moderately inflamed and slightly edematous throat and some coating of the tongue. The lymph nodes were neither enlarged nor tender. Dry crackling rales were heard throughout both lung fields. Respiration was normal. There were no areas of dulness. The remainder of the examination showed only varicosities of the legs and hyperactive reflexes.

A roentgenogram of the chest made twenty-four hours after onset of the illness showed in the hilar portion of the right lung an early infiltrating lesion. Supportive and symptomatic treatment was instituted, but the patient's condition gradually became worse. A second roentgenogram, made sixty-six hours after onset, showed dense infiltration radiating outward from the right hilus. September 9 administration of 1 Gm. of sulfadiazine every four hours was begun. September 10 the patient's condition was still worse with a temperature of 105.2 F., a pulse rate of 104 and respirations 64; the administration of sulfadiazine was discontinued, morphine given and the patient placed in an oxygen tent. September 10 the animals inoculated with the patient's sputum, collected sixteen hours after onset of the disease, were reported as suggesting tularemia; so that evening the patient received two 500 cc. transfusions of whole blood from immune donors and 60 cc. of Foshay's antitularemic serum in 1,000 cc. of 5 per cent dextrose in saline solution. During the night, however, she became more restless, more cyanotic and irrational. The blood pressure dropped from 145 systolic to 120 systolic and 110 diastolic. Early in the morning of September 11 respiration became quite rapid and weak, cyanosis deepened, and death occurred at 9:05 a. m., approximately four and one-half days after onset of illness.

On the morning of September 8 the blood gave a red cell count of 4,454,000, a hemoglobin content of 13.5 Gm. and a white cell count of 12,500. The differential count showed 80 neutrophils, of which 18 were stab forms, 19 lymphocytes and 1 a monocyte. Toxic granules were present in the neutrophils. The sedimentation rate was 51 mm. in one hour. Examination of sputum (smear and culture) showed a predominance of Streptococcus viridans; pneumococci were not found. Serum agglutination reactions for typhoid H, paratyphoid A, and paratyphoid B bacilli were positive to a dilution of 1:20. Culture of the blood, examination of the stool, dark field examination of the urine and serum agglutination tests with typhoid O, Brucella abortus, Proteus OX-19, P. tularensis, Leptospira canicola and Leptospira icterohaemorrhagiae as antigens gave negative results. Cultures of stool and urine were negative for pathogenic bacteria. The urine showed albumin (+++), 4 to 6 pus cells per high power field, many granular casts and an occasional red blood cell.

Autopsy.—External examination revealed nothing of significance. Each pleural space contained 30 to 40 cc. of yellowish fluid, and 20 cc. was present in the pericardial sac.

The left lung was soft and crepitant, and weighed 580 Gm. The cut surface showed congestion and edema throughout. The right lung weighed 820 Gm. There were marked edema and congestion of the upper and middle lobes. The upper portion of the lower lobe was completely consolidated, and over this portion there were

From the Pathology Laboratory, National Institute of Health, Bethesda, Md., and the Department of Pathology, United States Marine Hospital, Baltimore.

1. Simpson, W. M.: Arch. Path. **6**:553, 1928.

numerous petechial hemorrhages. On section of the lobe there was seen in the consolidated portion an oval area, measuring 3 by 5 cm., which appeared granular, more dense and of lighter color than the surrounding tissue. The hilar lymph nodes on the right side were moderately enlarged and anthracotic.

The aorta showed a little atherosclerosis.

The peritoneal cavity contained 140 cc. of yellowish fluid. The liver weighed 1,900 Gm.; it had a rather light color, and the cut surface showed yellowish mottling but no focal necrosis. The spleen weighed 220 Gm.; it had a soft pulp but showed no foci of necrosis.

With the exception of a small shallow, apparently inactive ulcer in the duodenum, the gastrointestinal tract was normal. The gallbladder showed considerable edematous thickening. The adrenal glands were congested, with a few small hemorrhages. The kidneys were not enlarged; the cut surfaces were congested, and there was some loss of demarcation between cortex and the medulla. The urinary bladder contained 350 cc. of urine. The pancreas was congested. A 7 mm. fibroid was present in the left cornu of the atrophic uterus. The heart, the ureters, the ovaries and the fallopian tubes were normal.

Microscopic Examination.—Lung: In the completely consolidated areas an apparent nodularity was seen under low power, produced by variation in the character of the exudate. Undulating and anastomosing bands in which the alveoli were filled with a largely fibrinous exudate separated areas in which the alveolar exudate was almost entirely cellular. This microscopic pseudonodular effect was heightened by the fairly sharp line between the alveoli with cellular and those with largely fibrinous exudate. The cellular exudate in some blocks showed marked karyorrhectic necrosis with loss of identity of the cells. Caseous necrosis of the exudate was not present, and necrosis of alveolar septums was seen in only a few small areas. In areas of less advanced karyorrhexis many cells were identified as large mononuclears, the nuclei being round, indented or lobated Also in such areas occasional to few polymorphonuclear leukocytes were seen. While fibrin was generally not present in these alveoli, a few showed thick and often fragmented fibrin strands. In the alveoli in which the copious fine-meshed fibrin formed the bulk of the exudate, cells were present usually in small numbers. These cells usually were well preserved and could be identified with certainty. Polymorphonuclear leukocytes and large mononuclear cells were present in about equal number, sometimes the one, sometimes the other type, predominating. The alveoli bordering the area of complete consolidation contained lesser amounts of fibrinocellular, serocellular or serous exudate. Here also the cells were well preserved and moderate numbers of polymorphonuclear leukocytes were identified. The somewhat thickened and edematous alveolar septums focally were infiltrated by a few lymphocytes and large mononuclears and were often covered by a continuous layer of hypertrophic cuboidal cells. In consolidated areas the small bronchi and bronchioles were filled with exudate similar to that in the alveoli, fibrin usually being abundant. The walls showed a loose structure, some edema and patchy infiltration by lymphocytes, mononuclears and fewer polymorphonuclear leuekocytes. In some the epithelium was absent from a portion of the wall, with the exudate lying directly on the basement membrane; necrotic epithelial cells were rare. The perivascular connective tissue, the interlobular septums and the pleura showed changes similar to those of the bronchial walls, with considerable variation in degree in different areas. The pleura was covered by a layer of laminated fibrin in which relatively few cells were present.

Two blocks of tissue from the grossly nonconsolidated portions of the lung showed small areas in which changes in the alveolar septums were similar to those at the border of consolidated areas, though less marked. In such areas the alveoli contained a little serum, fibrin or few to many cells. Although some of these were macrophages, polymorphonuclears usually were the most numerous.

Bronchial Lymph Nodes (right): These nodes showed a few focal lesions, the largest of which measured 2 mm. in diameter. Each lesion was formed of large mononuclear cells showing advanced karyorrhectic necrosis in the central part of the lesion. The lymphoid follicles were small, and there was moderate irregular reticuloendotheliosis of sinus and pulp. Many of the reticulum cells contained particles of carbon. Bacteria were not found.

Heart: A moderate number of muscle fibers showed epinuclear accumulation of brown granular pigment.

Liver: The central half to three fourths of all lobules of the liver showed narrowing of liver cell cords, corresponding widening of sinusoids, oxyphilia of the cytoplasm of liver cells, variable degrees of karyolysis, absence of some cells and frank necrosis of a few. In such areas there were a few to a moderate number of neutrophils between cell cords and sinusoids and in the sinusoids. In periportal areas the liver cells contained a few fine fat droplets. This graded to the center of lobules, where the fat was moderate in amount; here a few fat globules were large.

Kidney: A little oxyphilic coagulum was present in some glomerular spaces. The epithelial cells of convoluted tubules were large and granular. A very few small patches of interstitial cortical fibrosis were seen.

Spleen: The spleen showed moderate congestion of pulp and sinus with very slight irregular polymorphonuclear leukocyte infiltration. There was one lesion present in the pulp. It measured 500 microns in diameter and was similar to those in the lymph nodes. The follicles were small and showed no activity. Bacteria were not found.

Stomach and Duodenum: There was slight focal lymphocyte infiltration in the deep mucosa of the pylorus and among Brunner's glands of the duodenum.

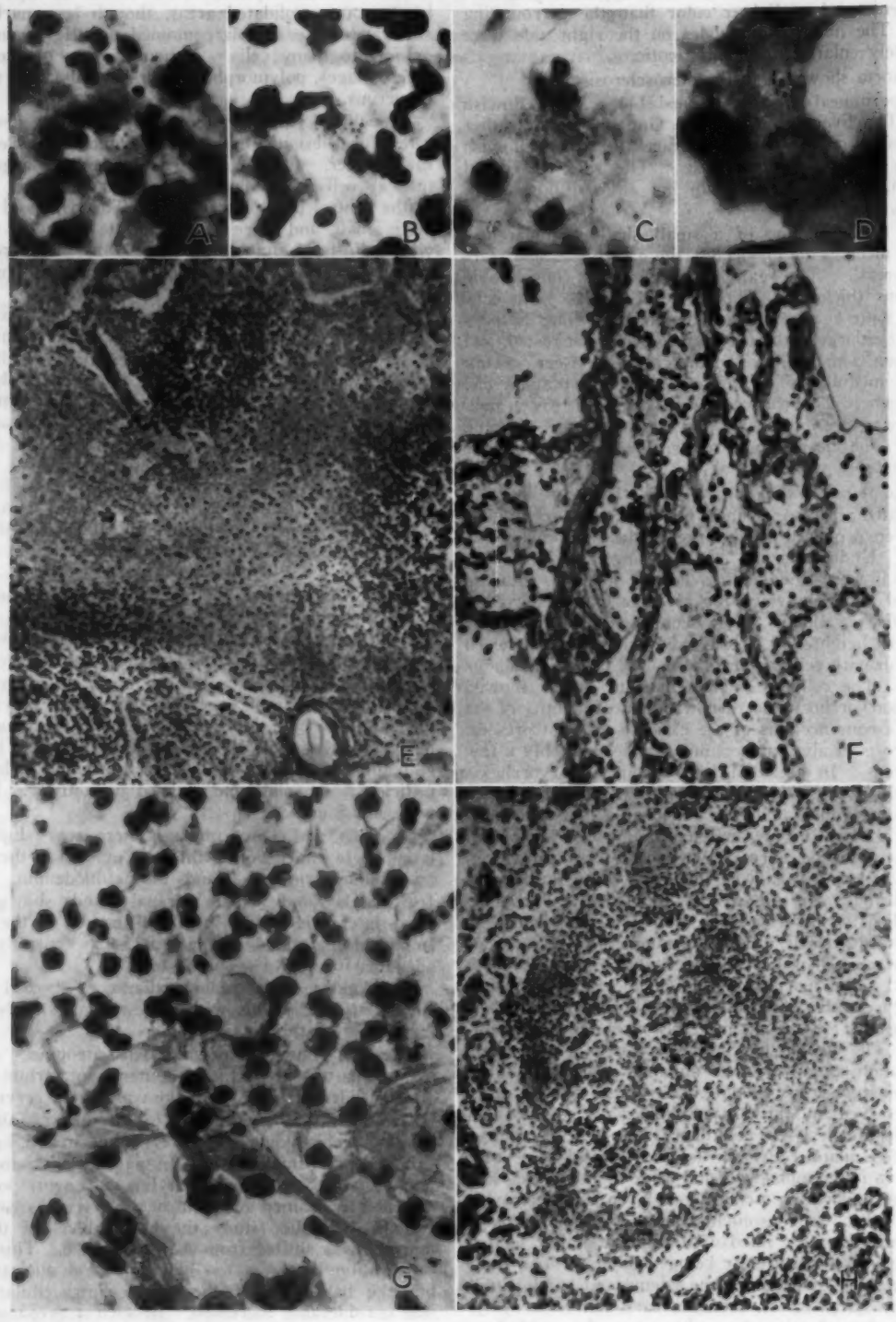
Adrenal Glands: The adrenal glands showed slight focal interstitial lymphocyte infiltration of the cortex. In one adrenal gland there was a 15 mm. centrally located adenoma formed of spongiocytes.

Gallbladder: The perimuscular coat showed marked edematous thickening with a few lymphocytes in the inner part of this layer.

Uterus: The endometrium was atrophic. A small leiomyoma was present in the outer myometrium. There was considerable fibrosis of the wall of the cervix.

Demonstration of Bacteria by Staining: All of the tissues for histologic study were fixed in a 3.8 per cent solution of formaldehyde. In paraffin sections of the lungs stained with hematoxylin and azure eosinate,[2] very faintly stained small intracellular bodies were seen. For their further study the buffer level of the stain mixture was shifted from p_H 4.6 to p_H 5. This gave a preparation that was too blue for good nuclear detail, but the basophilia of the minute intracellular bodies was considerably increased. In such a preparation the bacteria were seen as minute coccoid and coccobacillary forms and were gram negative. They were found in greater numbers in the cellular exudate showing only slight karyorrhectic necrosis. They were, however, seen frequently in the areas marginating the completely consolidated lung and in this location were found with greater ease since the exudate was well preserved. They

2. Lillie, R. D.: Stain Technol. **16**:1, 1941.



A, *B*, *C* and *D*, intracellular coccoid and coccobacillary organisms in exudate of pulmonary alveoli. *A*, *B* and *C*, × 1,000; *D*, 1,500. *E*, consolidated lung showing contrasting cellular and fibrinous exudate; × 100. The scattered cells enmeshed in fibrin are relatively well preserved. *F*, small area of recent pulmonary involvement; × 200. Many such areas were present in the grossly nonconsolidated portion of the lung. *G*, alveolar exudate in an area similar to that shown in *F*; × 775. The majority of the cells are polymorphonuclear leukocytes. *H*, focal lesion in bronchial lymph node; × 90.

occurred in both mononuclear cells and polymorphonuclear leukocytes, usually in small clusters. A few cells filled with the organisms were seen in scattered areas. Their distribution was patchy, and when one parasitized cell was found, others in the same alveolus also were likely to contain bacteria. They were found in cells of the bronchial exudate but were not seen in the swollen cells lining the alveoli. In identifying these organisms as P. tularensis, minute pigment granules, nuclear fragments and mast cell granules were seen and recognized as such. No other bacteria were observed.

Cultural Studies and Animal Inoculations.—This part of the investigation was made by Passed Assistant Surgeon Carl L. Larson. The following paragraphs are from his report:

"Specimens of sputum and blood were obtained on September 7, about sixteen hours after the onset of illness. Cultures of whole blood on dextrose–cystine–blood agar remained sterile, and mice inoculated with blood failed to show signs of illness. No cultures were made of the sample of sputum, but the specimen was emulsified in salt solution and injected subcutaneously into the guinea pigs and intraperitoneally into mice. These animals were ill on September 9 and cultures of P. tularensis were obtained from both guinea pigs and mice.

"Material taken at the autopsy was not cultured on mediums as it was thought that the tissues were contaminated. All were emulsified separately in salt solution and inoculated into guinea pigs. All these animals became ill between the third and the fifth day after inoculation and cultures of P. tularensis were obtained from animals inoculated with cardiac blood, liver, spleen and two specimens of lung tissue. No other material was examined."

COMMENT

The exact number of cases of death from tularemia in which autopsies have been made is difficult to determine since a few were included among collected cases as unpublished data and later were reported in detail by different authors. Including collected cases and original reports, Lillie and Francis [3] in 1936 and Foshay [4] in 1937 published pertinent data on 51 cases. Since that time we have found published reports of 22 cases in which necropsy was done,[5] making a total of 73. In all of these cases except that of Simpson [1] the duration of the disease was eight days or longer. In Simpson's case the duration was four days seven hours.

Certain evidence in this case suggests that infection took place by the upper respiratory route. The patient, a laboratory technician, did not handle the infected animals or cultures of the organisms. Cough and fever were among the first symptoms, and P. tularensis was demonstrated by animal inoculation in the sputum obtained sixteen hours after the onset of illness. At this time similar inoculation of blood gave negative results, and culture of the blood obtained forty hours after onset also gave negative results. It appears also that significance should be attached to the fact that only one lesion was found in the sections of spleen, whereas multiple and larger lesions were seen in the bronchial lymph nodes. Comparison of roentgenograms revealed pulmonary involvement twenty-four hours after the onset of illness. In our opinion, the circumstances and findings just related strongly suggest that pulmonary involvement was primary, with septicemia and involvement of bronchial lymph nodes and spleen secondary. It is realized that accidental ingestion of contaminated material must be considered in this case, but we find no evidence to support such a thesis.

The extent of the pulmonary involvement was much greater than that represented by the consolidated area seen on gross section. In paraffin sections made from the nonconsolidated portions, we noted some edema fluid, fibrin and variable numbers of cells in many alveoli, with associated swelling of the alveolar epithelium. Such involvement evidently contributed to the production of the cyanosis noted clinically. The microscopic observations on the lungs of this patient varied from those on the lungs of most patients whose cases have been published previously in showing more fibrin, absence of caseous necrosis and more polymorphonuclear leukocytes in the exudate. It is likely that the two latter variations are related to the short duration of the disease in that polymorphonuclears appeared to be more frequent and exudate much better preserved at the advancing margins of the pneumonic focus. It has been pointed out by some authors that karyorrhectic mononuclear cells may be mistaken for polymorphonuclears. This is indeed true, but our reference to these cells is based on their identification in well preserved exudate. The statement is often made that the presence of polymorphonuclears in significant numbers indicates a secondary infection with pyogenic bacteria. While this may be the explanation in many cases, the only bacteria found in the lung in this case were morphologically similar to P. tularensis. It is possible that early in the exudative process polymorphonuclears are fairly numerous and only later are overshadowed by the mononuclear reaction.

P. tularensis has been identified rarely in stained human tissues although prolonged search has been made for it with use of special staining procedures. Lillie and Francis [3] were unable to identify the organisms in their material.

3. Lillie, R. D., and Francis, E., in Lillie, R. D., and others: The Pathology of Tularemia, National Institute of Health Bulletin 167, United States Treasury Department, Public Health Service, 1936.

4. Foshay, L.: Arch. Int. Med. **60**:22, 1937.

5. (*a*) Pund, E. R., and Hatcher, M. B.: Ann. Int. Med. **10**:1390, 1937. (*b*) Mathews, W. R.: New Orleans M. & S. J. **90**:479, 1938. (*c*) Kimmelstiel, P., and Caldwell, H. W.: Am. J. Path. **15**:127, 1939. (*d*) Kitzmiller, K. V.: Ann. Int. Med. **12**:1375, 1939. (*e*) Ziferstein, I.: J. Iowa M. Soc. **30**:65, 1940. (*f*) Dredge, T. E.: M. Bull. Vet. Admin. **16**:337, 1940. (*g*) Blackford, S. D., and Casey, C. J.: Arch. Int. Med. **67**:43, 1941. (*h*) Ransmeier, J. C., and Schaub, I. G.: ibid. **68**:747, 1941. (*i*) Anschuetz, R. R.: Am. J. Dis. Child. **62**:150, 1941. (*j*) Kennedy, J. A.: J. A. M. A. **118**:781, 1942. (*k*) Thomas, H. B.: Ann. Int. Med. **17**:659, 1942. (*l*) David, J. K., Jr., and Owens, J. N., Jr.: Am. J. Dis. Child. **67**:44, 1944.

They had the opportunity to study tissue from some of their collected cases in which the finding of P. tularensis had been reported. They also were unsuccessful in identifying them in these tissues and pointed out that confusing basophilic bodies may occur in degenerating tissue, and that Gram stains should be made to exclude the gram-positive cocci. In the 22 cases with auotpsy [5] that we have found recorded since 1937, bacteria morphologically similar to P. tularensis were described in tissue sections in 1 case [5b] and in tissue smears (made at auopsy) in 3 others.[5k] We feel certain of the microscopic identification of the organisms in the lung of our patient, based on morphology and their occurrence in clusters in certain cells and supported by the fact that the organisms were recovered from sputum collected sixteen hours after the onset of illness and from lung tissue after death (animal inoculation).[6]

6. Drs. R. D. Lillie and Edward Francis examined the stained sections of lung in this case and agreed that the organisms were morphologically consistent with those seen in experimental animals.

The route of infection, the apparently primary pulmonary involvement, the short duration and the apparent lack of resistance on the part of the patient are probably related to the facility with which the organisms were demonstrated in the lungs.

SUMMARY

In the case of laboratory tularemia with autopsy reported the evidence suggests that infection took place by the upper respiratory route. P. tularensis was demonstrated in the consolidated lung. No other organisms were found. A few necrotic foci were observed in the bronchial lymph nodes and one in the spleen. There was centrolobular degeneration of the liver but no focal lesions. P. tularensis was isolated by animal inoculation from the sputum sixteen hours after onset and from the lung, the liver, the spleen and the cardiac blood at autopsy. Inoculation of animals with blood and culture of blood on the first day of illness and on the second day gave negative results.

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General Reviews

INTRACRANIAL VASCULAR TUMORS AND MALFORMATIONS

HAROLD H. NORAN, M.D., PH.D.
MINNEAPOLIS

Since the monographic studies of Cushing and Bailey,[1] Lindau [2] and Bergstrand, Olivecrona and Tönnis,[3] a most extensive literature has accumulated on the subject of vascular tumors of the intracranial cavity. Although much progress has been made in knowledge of the clinical and pathologic features of these lesions, yet much confusion remains, as indicated by the multiplicity of nomenclature and classification. Many different vascular lesions have been recorded under the same title, whereas similar lesions have been recorded under a wide variety of titles. Furthermore, a large number of the classifications that have been presented for these vascular tumors are conflicting. This almost complete lack of standardization in nomenclature and classification has made the evaluation of the already abundant literature highly difficult.

Nevertheless a comprehensive evaluation of the literature is warranted in order that one may arrive at some correlation between these various nomenclatures and classifications.

NATURE OF THE VASCULAR TUMORS

There are two main types of vascular tumors. They are referred to as angioma and angioblastoma. Angioma is a tumor composed of blood vessels of adult structure, while angioblastoma is comprised of embryonic vascular channels and proliferating vasoformative cells.

A prodigious amount of discussion has been recorded as to whether or not the tumors called angioma are true neoplasms or mere malformations. Cushing and Bailey,[1] Raney and Courville,[4] Levine,[5] Luschka,[6] and Dandy [7] were among those who expressed the belief that these tumors represent congenital anomalies. Globus [8] and Laidlow and Murray [9] postulated that angioma arose from a vestigial structure or a phylogenetic remnant, such as the gill arch. Schück [10] agreed that it was the result of faulty development but felt that it was capable of spontaneous and autonomous expansile growth. A number of authors have employed the term "hamartoma" instead of "angioma." Schmolck,[11] and Albrecht [12] defined the term "hamartoma" as designating a tumor-like anomaly, thereby evading the issue. Turner and Kernohan [13] also used this term but regarded the lesion as a pure malformation. They stressed the belief that angioma increases in size by enlargement of its individual vessels rather than by actual growth. Moolten,[14] on the other hand, expressed the opinion that hamartoma is capable of becoming cancerous and regarded angioblastoma as hamartoma rather than angioma. Bergstrand and his co-authors [3] concluded that angioma is a true tumor since it often becomes a space-consuming lesion. Schwartz [15] agreed since he regarded it as an autonomous new growth of tissue, thereby fulfilling Ewing's definition of a tumor. Virchow,[16] Ribbert,[17]

From the Department of Neuropsychiatry and the Department of Pathology, University of Minnesota Medical School.

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16. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, vol. 3, lect. 25, p. 460.

(Footnotes continued on next page)

Simmonds [18] and Heine [19] also expressed the opinion that angioma is a real neoplasm.

In general, most writers view the tumors called angioblastoma as true neoplasms exhibiting cellular proliferation. Turner and Kernohan,[13] however, have stated that angioblastoma might arise from hamartoma or a congenital anomaly. Bergstrand and his co-workers [3] cited an example of angioblastoma in a stillborn infant as evidence favoring the belief that the lesion is congenital. They further pointed out the frequent concomitant ocurrence of obvious congenital anomalies in other organs.

From this discussion it becomes apparent that at present it is impossible to state definitely whether angioma or even angioblastoma is a simple or a cancerous growth; they present characteristics of both malformations and neoplasms. The term "hamartoma" is not satisfactory, for it has been used to designate a miscellaneous group of lesions and adds nothing to present knowledge of vascular tumors.

CLASSIFICATION OF THE VASCULAR TUMORS AND MALFORMATIONS

A review of the classifications in the literature clearly portrays the lack of agreement regarding the basic structure of the individual lesions and also points out the frequency of conflicting nomenclatures. In general, these classifications have lacked uniformity and thus have served merely to add further confusion to an already extensive literature.

The classification offered by Cushing and Bailey has been widely quoted and is generally followed rather closely, especially in this country. It is as follows:

I. Vascular malformations.
   1. Telangiectasis (a group of capillaries).
   2. Angioma venosum (lesions composed principally of veins).
   3. Angioma arteriale (lesions containing vessels resembling arteries as well as veins).

II. Hemangioblastoma (angioblastoma).
   1. Cystic type (associated with cyst formation).
   2. Solid type (not associated with cyst formation).

Each of these two types was again classified into capillary, cellular and cavernous varieties according to the microscopic features.

The presence of brain tissue between the component vessels of angioma was of paramount importance in leading these investigators to conclude that it was an anomaly or a malformation rather than a neoplasm. Since material for histologic study was not available in most of their cases, the structure of the vessels comprising the angioma was ascertained merely from the resultant clinical manifestations or by a superficial examination of the lesion at operation. They made no distinction between the angioma which was confined to the meninges and the angioma which extended deeply into the cerebral parenchyma, probably because of the paucity of autopsy studies. The lesion comprised of only a few anomalous vessels was not separated from the one composed of an extensive congeries of vessels, replacing much of the brain parenchyma. Moreover, the authors inferred that the well known cavernous type of angioma, which consists of closely packed dilated vascular sinuses, was a variety of angioblastoma, and consequently they provided no place for this type of lesion in their classification.

Turner and Kernohan [13] in studying a large series of vascular neoplasms of the spinal cord suggested the following classification:

I. Vascular malformations.
   1. Telangiectasis.
   2. Angioma or hamartoma.
      (*a*) Angioma venosum.
      (*b*) Angioma arteriovenosum or angioma arteriale.

II. Vascular neoplasms.
   1. Capillary.
      (*a*) Capillary hemangioma.
      (*b*) Hemangioendothelioma.
      (*c*) Capillary hemangioblastoma.
   2. Cavernous.
      (*a*) Cavernous hemangioma.
      (*b*) Cavernous hemangioblastoma.
   3. Hemangiosarcoma.

Except for the use of the term "hamartoma," the first part of this classification is similar to that of Cushing and Bailey. They attempted to divide the tumors termed angioblastoma into groups manifesting various degrees of histologic malignancy. The capillary hemangioma consisted mainly of capillaries. The hemangioendothelioma was comprised not only of capillaries but of a few proliferating endothelial cells in the intervascular areas. In capillary hemangioblastoma the intervascular regions contained many more proliferating cells. The cavernous hemangioma and hemangioblastoma showed similar structures except that they contained numerous cavernous spaces. The hemangiosarcoma was a vascular tumor showing evidence of rapid growth. The terminologic scheme of the second group differs from that generally accepted, for all these lesions, as a rule, are regarded merely as angioblastoma. The true cavernous angioma was omitted as in

17. Ribbert, H.: Virchows Arch. f. path. Anat. **151**: 381, 1898.
18. Simmonds, M.: Virchows Arch. f. path. Anat. **180**:280, 1903.
19. Heine, L.: Ztschr. f. Augenh. **51**:1, 1923.

the classification of Cushing and Bailey. Finally, no distinction was made between the purely meningeal lesion and that involving the parenchyma.

Rienhoff's [20] classification has not been widely used.

1. Arterial aneurysm (tumor consisting of arteries).
2. Venous aneurysm (tumor comprised of veins).
3. Arteriovenous aneurysm (tumor containing both arteries and veins).

The use of the term "aneurysm" is not satisfactory, for it confuses the tumors ordinarily termed angioma with simple aneurysms of the cerebral arteries as well as with the traumatic fistula between the internal carotid artery and the cavernous sinus. The latter is often termed an arteriovenous aneurysm.

Dandy published the following classification, which is frequently referred to in the literature.

I. Arteriovenous aneurysm.

II. Venous abnormality.

1. Venous abnormality in the brain or venous anomaly.
2. Venous abnormality in the dura.
3. Angioma.
   (*a*) Cyst with angioma in the wall (actually angioblastoma).
   (*b*) Cavernous angioma.
   (*c*) Plexiform angioma (venous angioma).

This classification is not based on the actual pathologic structure of the lesions. Among the venous abnormalities of the brain and the dura were included lesions comprised of anomalous veins showing little increase in their size and number. Under angioma were listed venous tumors (plexiform angioma), but for some reason the arteriovenous tumors were called arteriovenous aneurysms. Dandy incorrectly regarded the cystic form of angioblastoma as angioma and left no place in his classification for the solid or only partly cystic angioblastoma.

Bergstrand, Olivecrona and Tönnis [3] worked out a classification which has appeared in many publications and is often followed in foreign literature.

1. Angioma cavernosum.
2. Angioma racemosum (a grapelike cluster of vessels).
   (*a*) Telangiectasis.
   (*b*) Sturge-Weber syndrome (a condition consisting of an angioma of the surface of the brain with calcification of the underlying cortex and an ipsilateral facial nevus).
   (*c*) Angioma racemosum arteriale (a grapelike cluster of vessels exclusively arterial).
   (*d*) Angioma racemosum venosum (a congeries of vessels resembling veins).
   (*e*) Arteriovenous aneurysm (a mass of inextricable vessels resembling arteries and veins).
3. Angioreticuloma (angioblastoma).
4. Angioglioma (a combination of glial and vascular elements).

This is the most comprehensive classification found in the literature. It is questionable, however, if telangiectasis should be regarded as racemose angioma. In addition, it seems unwise to place Sturge-Weber disease in this same group, for the calcification and degeneration of the involved cortex are the most significant lesions both clinically and pathologically. These authors questioned the existence of the arterial racemose angioma. As in other classifications, no distinction was made between the lesions limited to the meninges and those involving the brain parenchyma. The term "arteriovenous aneurysm" was also employed here for arteriovenous angioma. The name "angioreticuloma" was certainly no improvement over the more widely accepted "angioblastoma."

Russel [21] offered the following classification:

1. Cirsoid aneurysm (lesions generally termed racemose angioma).
2. Capillary hemangioma (angioblastoma).
3. Capillary telangiectasis (telangiectasis).
4. Cavernous hemangioma.

This classification is more general than those already listed. The nomenclature, however, is confusing. The term "capillary hemangioma" is certainly more suggestive of telangiectasis, for example, than of angioblastoma.

The classification used by Virchow is often mentioned in the literature.

1. Cavernous angioma.
2. Angioma simplex (telangiectasis).
3. Telangiectatic tumor formation (false angioma).
4. Angioma racemosum.

There is a definite resemblance to the better known classification presented by Bergstrand, Olivecrona and Tönnis. Angioblastoma would probably be classified as false angioma.

The following classification of vascular lesions was published by Bort.[22]

1. Aneurysm (a simple aneurysm of an artery—not an angioma).
2. Serpentine aneurysm (angioma racemosum arteriale or an extensive simple aneurysm).

20. Rienhoff, W. F., Jr.: Bull. Johns Hopkins Hosp. **35**:271, 1924.

21. Russel, D.: Proc. Roy. Soc. Med. **24**:383, 1931.

22. Bort: Beitrag zur Kenntnis des Angioma racemosum des Gehirns, Inaug. Dissert., Leipzig, Arb. a. d. Geb. d. path. Anat. Inst. zu Tübingen, 1920.

3. Serpentine angioma (venous or arteriovenous angioma).
4. Arterial racemose angioma (a congeries of arteries and probably veins).
5. Venous racemose angioma (a plexus of veins).
6. Racemose varix (probably similar to the foregoing type, being composed of a congeries of varices but no doubt also includes cavernoma).
7. Varix (a simple dilatation of a vein or a venous anomaly).

This classification is extremely difficult to follow, as Bort's description of the various types of lesions is not clear. The use of the terms "serpentine aneurysm" and "serpentine angioma" is confusing. Although the racemose varix is probably comprised largely of cavernous angioma, the term is readily confused with "venous racemose angioma." This is the only classification that clearly recognizes the most simple venous anomaly or varix. Bort completely neglected to mention telangiectasis and angioblastoma.

Benda [23] classified the venous tumors as follows:

1. Phlebectasia (a diffuse widening of a vein).
2. Varicosity (a diffuse irregular dilatation with circumscribed ampullar or saclike formations).
3. Venous angioma (a circumscribed conglomeration of veins).

This classification deals only with lesions comprised of veins. Phlebectasia and varicosity are the more simple venous anomalies which differ only in the distribution of the vascular dilatations and are similar to the varix in Bort's classification.

Vascular Tumors of the Meninges.—These lesions are of two general types: one is angiomatous meningioma, which is a meningeal tumor composed of adult vascular elements, including arteries, veins, capillaries or cavernous spaces; the second is angioblastic meningioma, which has a structure similar to angioblastoma as found within the cerebellum. Because of the structural similarity of these angioblastic lesions of the meninges to the parenchymal lesions, they were classified with the vascular tumors by Bailey and Ford.[24] Cushing and Eisenhardt,[25] on the other hand, regarded them as meningioma, basing their opinion on the gross and clinical features rather than on the microscopic characteristics.

Globus [8] classified the angiomatous lesions of the meninges with meningioma, while Cushing and Bailey,[1] as well as others, included them with cerebral angioma probably because their material was operative and no separation was possible in the absence of postmortem studies.

Because of these conflicting opinions regarding the nature of the vascular meningeal lesions, a brief discussion of their classification is indicated. Cushing and Eisenhardt [25] listed the angioblastic meningeal tumors under their meningioma type IV, which was divided into three variants as follows:

Variant 1. Incompletely differentiated, with mitoses. (It is a cellular tumor showing histologic evidence of rapid growth.)

Variant 2. Transitional between the meningothelial type and angioblastoma. (It shows transitions toward the meningothelial meningioma.)

Variant 3. Angioblastoma (capillary or cellular). (It has the typical structure of angioblastoma.)

All the lesions revealed a predominating angioblastic structure as well as a typical network of reticulum. No mention was made of the angiomatous meningioma.

Courville and Abbott [26] offered the following classification:

1. Meningeal angioblastoma.
2. Transitional angioblastoma.
3. Angioblastic meningioma.
4. Combined meningotheliomatous-angioblastic meningioma.

This classification is difficult to follow because of its redundancy. Certainly the combined meningotheliomatous-angioblastic type is actually the transitional angioblastoma. Such a separation results only in confusion. Moreover, this classification is similar to that of Cushing and Eisenhardt [25] and therefore serves only to complicate the literature.

Globus [8] classified the vascular meningeal tumors with meningioma and subdivided them into the angioblastic and the angiomatous type. His classification is as follows:

Meningioma piale (pial or vascular meningioma).

1. Hemangioendotheliomatous subtype (angioblastic meningioma also includes angioblastoma situated within the neural parenchyma).
2. Hemangiomatous subtype (angiomatous meningioma).

This is the most comprehensive classification of the vascular meningeal tumors, for it also includes those comprised of adult vessels. This classification of the intracerebral or intracerebellar angioblastic tumors with meningioma is

23. Benda, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie, Berlin, Julius Springer, 1924, vol. 2.

24. Bailey, O. T., and Ford, R.: Am. J. Path. **18**: 1, 1942.

25. Cushing, H., and Eisenhardt, L.: Meningiomas, Springfield, Ill., Charles C Thomas, Publisher, 1938.

26. Courville, C. B., and Abbott, K. H.: Bull. Los Angeles Neurol. Soc. **5**:47, 1940.

not in keeping with the present day concept of cerebral tumors.

PATHOLOGIC STUDY OF THE INDIVIDUAL VASCULAR LESIONS

From a survey of the literature it becomes obvious that there are a number of vascular lesions occurring within the intracranial cavity whose structural characteristics suggest that they might be distinct entities. The available literature concerning these lesions is most conflicting and offers little help in suggesting some orderly manner of thinking about them. Thus, in order to arrive at a satisfactory classification, one should be comprehensive and consider not only the pathologic structure of these lesions, which shows overlapping of many types, but also the clinical features. Although the latter are obviously important, space will permit no more than a brief reference to the clinical characteristics of each lesion. Consequently, this paper will be restricted principally to pathologic aspects. It seemed possible that such a broad consideration when applied to the extensive available literature and augmented by a review of the cases observed in the departments of neuropsychiatry and pathology of the University of Minnesota Medical School might result in some success in suggesting a practical method of understanding these vascular lesions from a clinicopathologic point of view. In order to begin with a most unbiased approach, each type of intracranial vascular tumor will be considered separately and individually and then an attempt will be made to find some orderly classification based on the observations. The following lesions are the ones considered in this review:

1. Telangiectasis (dilated capillaries).
2. Rendu-Osler disease (familial telangiectasia or generalized angiomatosis).
3. Cerebral varix (simple anomalous veins similar to varicosities).
4. Sinus pericranii (vascular tumor of the forehead or the scalp communicating with the superior sagittal sinus).
5. Cavernoma or cavernous angioma (closely packed large vascular spaces).
6. Venous (racemose) angioma (cluster of vessels resembling veins).
7. Arterial (racemose) angioma (a congeries of arteries).
8. Arteriovenous (racemose) angioma (a congeries of arteries and veins).
9. Angiomatous meningioma (adult blood vessel tumor of the meninges).
10. Sturge-Weber disease (characterized by a facial nevus associated with cerebral calcification and angiomatosis of the overlying meninges).
11. Angioblastoma (primarily a cerebellar tumor composed of embryonic vascular elements).
12. Lindau's (von Hippel's) disease (angioblastoma of the retina and the nervous system).
13. Angioblastic meningioma (embryonic vascular tumor of meninges).
14. Angiosarcoma (angioblastic tumor showing rapid growth).
15. Angioglioma (a combination of adult vascular and glial elements).

The material in the departments of neuropsychiatry and pathology of the University of Minnesota Medical School consists of 39 cases of vascular tumors. A pathologic investigation of the lesions was made in all but 2 cases. In these 2 instances, a case of sinus pericranii and a case of Sturge-Weber disease, the diagnosis was obvious without pathologic studies. The following staining technics were employed in determining the anatomic structure of the tumors: hematoxylin and phloxine stain, Mallory-Heidenhain azocarmine stain, Holzer stain for glia, Nissl stain, Perdrau stain for reticulum, Bodian silver stain for axons, Weigert-Van Gieson and Weigert elastic tissue stains.

TELANGIECTASIS

Introduction.—The term "telangiectasis" designates a small lesion composed of a collection of dilated capillaries. A number of cases of telangiectasis have been reported in the literature, and, surprisingly enough, little conflict of terminology is found, most authors using the term "telangiectasis." However, vascular tumors which are distinctly different structurally from this lesion have been described as telangiectasis by Michael and Levin,[27] Oppenheim,[28] Broeckaert[29] and others. A number with a suggestion of a transitional tendency toward cavernous angioma appeared under the title of cavernoma or cavernous angioma, and a few probably were true transitional forms (Schmidt[30]; Beitzke[31]; Baum[32]; Schweyer[33]; Uyematsu[34]; Schley[35]; Malamud[36]).

27. Michael, J. C., and Levin, P. M.: Arch. Neurol. & Psychiat. **36**:514, 1936.
28. Oppenheim, H.: Neurol. Centralbl. **32**:3, 1913.
29. Broeckaert, J.: Bull. Acad. roy. de méd. de Belgique **22**:360, 1908.
30. Schmidt, O.: Beitr. z. klin. Chir. **118**:178, 1920.
31. Beitzke, H.: Charité-Ann. **31**:360, 1906.
32. Baum: München. med. Wchnschr. **58**:411, 1911.
33. Schweyer, H.: Arb. a. d. Geb. d. path. Anat. u. Bakt. **8**:145, 1914.
34. Uyematsu, S.: J. Nerv. & Ment. Dis. **52**:388, 1920.
35. Schley, W.: Virchows Arch. f. path. Anat. **265**: 665, 1927.
36. Malamud, W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **97**:651, 1925.

The lesion is almost always silent clinically, but on rare occasions symptoms may be produced as a result of a rupture of one of the small vessels (Michael and Levin [27]). A few published cases suggest hereditary factors; however, the evidence for this is weak (Kufs [37]; Oppenheim [38]; Michael and Levin [27]).

Gross Pathology.—Telangiectasis is a rather small, poorly circumscribed lesion which may be found in almost any part of the nervous system. It is common in the cerebrum, where it may be situated within the cortex, the white matter or the basal nuclei. It usually occurs deep within the cerebral parenchyma and rarely reaches the brain surface. An exception was reported by Jaffé,[38] in which multiple telangiectasis was encountered in the meninges and the spinal nerve rootlets. Telangiectasis is also found within the brain stem, where it shows a predilection for the pons, according to Ohlmacher,[39]

TABLE 1.—*Cases of Intracranial Telangiectasis Studied in the Departments of Neuropsychiatry and Pathology of the University of Minnesota Medical School*

Case	Sex	Age, Yr.	Symptoms	Gross Appearance	Location
1	M	51	Silent	Resembled petechiae	Frontal lobe
2	M	60	Silent	Hemorrhagic lesion	Globus pallidus
3	M	57	Silent	Focus of tiny hemorrhages	Temporal lobe
4	M	57	Silent	Conglomeration of small engorged vessels	Basal ganglions and midbrain

Schley,[35] Sommerfelt,[40] Leyser [41] and others. In a few cases it has been reported located within the spinal cord (Claude and Loyez [42]; Hadlick.[43]). It usually occurs as a single isolated lesion, but multiple involvement is not unusual. In the latter case the lesions may be restricted to one relatively localized region of the brain or may be widely disseminated. As many as 30 lesions have been discovered in a single patient (Huebschmann [44]).

The lesion is sometimes rather inconspicuous and might be readily overlooked. Its appearance in the cases tabulated here most commonly suggested a focal collection of petechiae. Occasionally one can grossly identify the tiny vascular spaces filled with blood (case 4). Even though the lesion strongly resembles petechiae, rupture of the vessels with extravasation of blood is extremely rare, and only 1 case of this kind has been found recorded in the literature (Michael and Levin [27]).

Microscopic Anatomy.—The lesion consists of a collection of numerous engorged capillaries or cavernous spaces which are always separated by various amounts of relatively normal brain tissue. The capillaries may be small, but larger cavernous spaces may be prominent. Regardless of the size of the vessel, its wall consists of a single layer of flat endothelium, which occasionally is surrounded by a thin rim of collagenous tissue. Smooth muscle and elastic elements are never present. The vessels, as a rule, are not so numerous that they replace any significant amount of brain tissue or produce any notable alterations in the regional neural parenchyma.

RENDU-OSLER DISEASE

Introduction.—Rendu-Osler disease is a rare familial condition in which telangiectatic lesions are disseminated over the skin and may involve various internal organs. The nervous system generally is not implicated, but a few cases of neural involvement have been reported. Therefore, it becomes necessary to review this syndrome briefly.

A number of terms have been used for this disease. It has most often been referred to as familial telangiectasia or generalized angiomatosis. Although it was first described by Sutton [45] in 1864, it was named after Rendu [46] and Osler,[47] who published their cases at a later date.

Pathologic Features.—The individual lesions are quite typical of telangiectasis regardless of their location. The lesions of the skin are commonly present at birth and increase with age. They are red to purple and vary considerably in size but seldom do they exceed a few millimeters in diameter. Telangiectasis commonly involves the mucous membranes of the respiratory and gastrointestinal tracts and the urogenital system. Hemorrhage from the lesions is common, and the clinical symptoms are the result of this bleeding.

37. Kufs, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:651, 1928.
38. Jaffé, R. H.: Arch. Path. **7**:44, 1929.
39. Ohlmacher, A. P.: J. Nerv. & Ment. Dis. **26**: 395, 1899.
40. Cited by Bergstrand, Olivecrona and Tönnis.[3]
41. Leyser, E.: Monatschr. f. Psychiat. u. Neurol. **51**:83, 1922.
42. Claude, H., and Loyez, M.: Rev. neurol. **19**:181, 1911.
43. Hadlick, R.: Virchows Arch. f. path. Anat. **172**: 429, 1903.
44. Huebschmann: Deutsche Ztschr. f. Nervenh. **72**: 205, 1921.
45. Sutton, H. G.: M. Mirror, London **1**:769, 1864.
46. Rendu: Bull. et mém. Soc. méd. d. hôp. de Paris **13**:731, 1896.
47. Osler, W.: Bull. Johns Hopkins Hosp. **12**:333, 1901.

Lesions of the central nervous system are silent clinically unless they produce intracerebral or subarachnoid bleeding. Cases of the disease with verified cerebral involvement have been recorded by Archer [48] and Goldstein.[49] Generally there are many persons in the family for several generations afflicted with this condition.

CEREBRAL VARIX

Introduction.—This lesion consists of abnormal, dilated, thin-walled vessels situated either within the brain substance or on its surface. Schaltenbrand [50] reviewed the literature and was able to find reports of only 13 cases in addition to his own. The vascular abnormalities are most frequently referred to as varices or varicosities. Dandy [7] in reporting cases of varices of the superior sagittal sinus incorrectly called the varices dural aneurysms, while Cushing and Bailey [1] classified their 2 cases with cases of venous angioma. Benda [28] advanced the title "phlebectasia."

TABLE 2.—*Cases of Cerebral Varices Studied in the Departments of Neuropsychiatry and Pathology of the University of Minnesota*

Case	Sex	Age, Yr.	Symptoms and Findings	Gross Appearance	Location
5	F	53	Silent	Not visible	Subcortical white matter of cerebrum
6	F	47	Headache, confusion, paresis of left upper limb, stupor	Subarachnoid bleeding, a large collection of varices with vascular channels connecting with the straight sinus	Surface of right occipital lobe
7	F	73	Vomiting, diplopia, visual hallucinations, papillitis, partial deafness, disorientation, stupor	Ventricular and subarachnoid hemorrhage; varices overlooked on gross examination	Cerebellum and region of pineal gland

The lesions may be clinically silent and hence may be discovered accidentally at autopsy (case 5). In many cases, however, clinical symptoms do occur but are usually the result of intracranial hemorrhage or, less commonly, of vascular thrombosis eventuating from the varix.

Gross Pathology.—Varices are often not visible on gross examination or may frequently be overlooked because of their small size (cases 5 and 7). In a number of cases, however, they are sufficiently large to be seen readily (case 6) and may even measure several centimeters in diameter (Beger [51]). In all the cases tabulated in this section multiple anomalous vessels comprised the lesions. The number of vessels in a lesion is, as a rule, not large; occasionally one encounters a varix consisting of a single large vessel (Guldenarm and Winkler [52]; Pfannenstiehl [53]; Beger [51]; Wohak [54]; Marx [55]). There is no site of predilection. In fact, the varix may occur in any location within the brain or on its surface, frequently involving even the dural sinuses (Wohak [54]; Marx [55]; Dandy [7]). In the latter case there is a large vascular dilatation which may cause partial erosion of the overlying skull and occasionally softening of the adjacent cerebral tissue. The dural sinuses may be involved directly by the varix or may be connected with it by means of anomalous vascular channels (case 6).

The most common complication of the intracerebral varix is an intracranial hemorrhage (cases 6 and 7). Depending on the location of the abnormal vessel which ruptures to produce the bleeding, blood may extravasate into the brain tissue, the subarachnoid space or the ventricular system.

Microscopic Anatomy.—The cerebral varix shows a rather characteristic histologic picture. It consists of a relatively large thin-walled vessel, usually lined by a single layer of endothelium and encircled by a relatively thin lamina of fibrous connective tissue (fig. 1). The latter often undergoes hyaline degeneration. Muscle fibers and elastic elements are generally absent (Schaltenbrand [50]; Esser [56]). These vessels frequently resemble the large vascular spaces of cavernous angioma, but in contrast to the latter the varicose vessels are separated from one another by cerebral parenchyma. This regional cerebral tissue may be intact or may show rather prominent degenerative and reactive alterations.

When muscle or elastic tissue is found in the wall of the varix, these elements are less prominent than in normal veins. A lesion showing this kind of vascular structure presents a vague

48. Archer, cited by Goldstein, H. S.: Arch. Int. Med. **27**:102, 1921.

49. Goldstein, H. S.: Internat. Clin. **3**:148, 1930.

50. Schaltenbrand, W.: Frankfurt. Ztschr. f. Path. **52**:363, 1938.

51. Beger, H.: Virchows Arch. f. path. Anat. **231**: 439, 1921.

52. Guldenarm, J. A., and Winkler, C.: Nederl. tijdschr. v. geneesk. **27**:217, 1891.

53. Pfannenstiehl: Centralbl. f. Gynäk. **11**:601, 1887.

54. Wohak, H.: Virchows Arch. f. path. Anat. **242**: 58, 1923.

55. Marx, A. M.: Med. Klin. **21**:1612, 1925.

56. Esser, A.: Verhandl. d. deutsch. path. Gesellsch. **20**:411, 1925.

resemblance to racemose angioma. However, in the varices, vessels of relatively typical arterial or venous structure are never seen, and the vessels are less numerous and more uniform in structure than the numerous irregular, most variable elements of racemose angioma.

The usual complication in this lesion is a rupture of the varix wall with a resulting cerebral

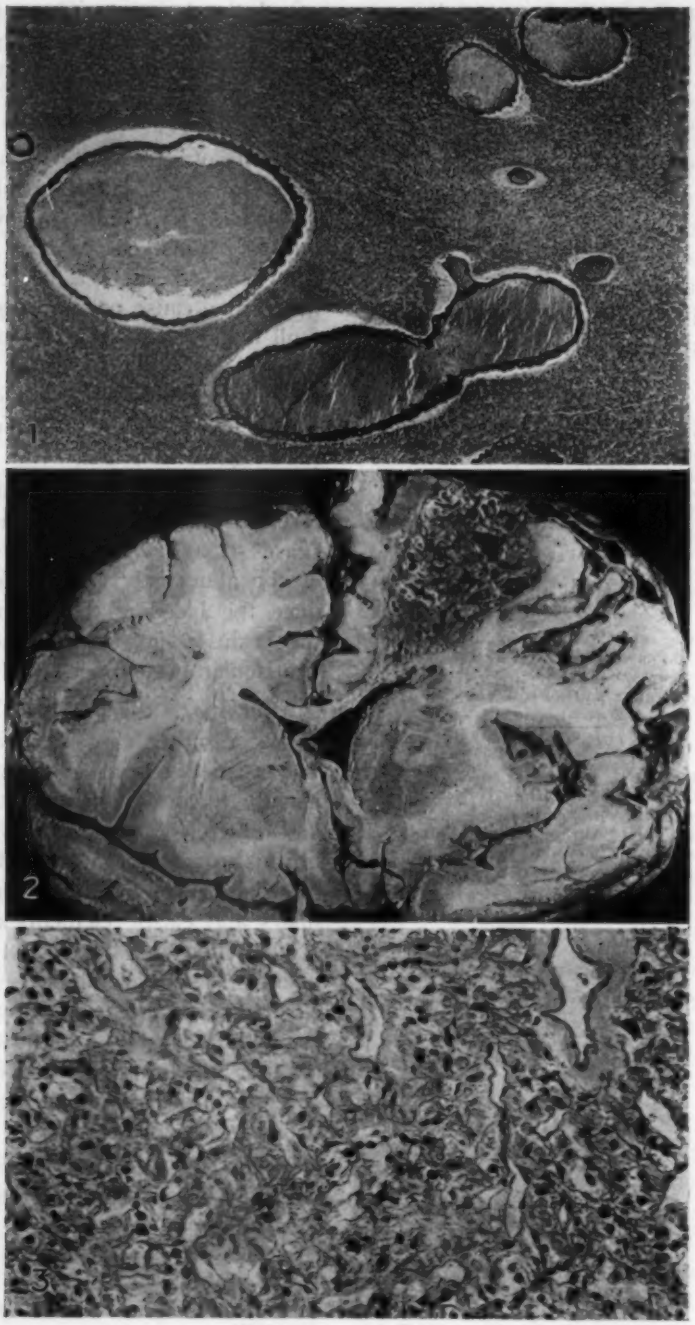

Fig. 1.—Small intracerebral varices. Note the large dilated vascular spaces separated by intact cerebral tissue. The vessel walls are thin, consisting of a flat endothelial lining and a thin layer of fibrous connective tissue. Weigert-Van Gieson stain.

Fig. 2.—The characteristic appearance of venous angioma is observed in the cone-shaped mass of angiomatous vessels extending deep into the cerebral hemisphere. Note the large tortuous vessels over the surface of the lesion, which course along the meninges of the neighboring regions of the brain for some distance.

Fig. 3.—Cerebellar angioblastoma demonstrating numerous small vascular spaces separated by proliferating endothelial cells. Hematoxylin and eosin stain.

hemorrhage. Thrombosis with hemorrhagic infarction was encountered in Amsler's [57] third case and my case 6.

The etiologic nature of the intracranial varices has occasioned much speculation. Most authors (Anders,[58] Kallenberger,[59] Kaufman,[60] Orth [61] and others) have thought that they resulted from a congenital weakness of the vessel walls, but others have postulated that they eventuated from an earlier venous inflammation (Beger [51]), from prolonged trauma over bony ridges (Amsler [57]; Fisher [62]) or from mechanical factors eventuating from abnormal presentation of the head during birth.

SINUS PERICRANII

Introduction.—Sinus pericranii is a vascular tumor which, as a rule, protrudes from the forehead and communicates with the superior sagittal sinus. Although this lesion is largely outside the skull, it should be considered with the intracranial vascular lesions because of its connection with the superior sagittal sinus and its occasional production of cerebral symptoms. For some reason, most authors when discussing the vascular neoplasms of the brain fail to mention this condition.

The lesion was first described in 1760 by Percival Pott [63] and later was termed sinus pericranii by Stromeyer.[64] Hahn [65] in 1928 reviewed the literature, discovering 84 recorded examples.

Clinically, sinus pericranii in many cases produces no symptoms other than the tumor of the forehead. The tumor appears early in life and may enlarge slowly over a period of many years. It is soft and compressible. Anything that increases the intrathoracic or the venous pressure, such as coughing or straining and lowering the head, causes the tumor to enlarge. In rare cases, variable cerebral symptoms, including increased intracranial pressure and a cerebral bruit, have been described.

Gross Pathology.—The tabulated case was not studied pathologically, and unfortunately few careful pathologic studies have been published. In a majority of cases the tumor was situated in the midportion of the forehead as in the case tabulated, but almost any point along the superior sagittal sinus as far back as the occipital region has been involved in occasional instances (Wakely). A defect occurs in the underlying cranial bones allowing the lesion to communicate with the adjacent dural sinus. The appearance of the actual lesion is that of a congeries of small and large vascular spaces, often resembling cavernous angioma. In fact, it is likely that a number were similar to cavernous angioma (Mueller [66]).

Microscopic Anatomy.—Generally there are numerous thin-walled vascular spaces, which are of irregular contour and are embedded in fibrous connective tissue. The spaces are connected with one another by a multiplicity of small anastomotic vascular channels having the structure of capillaries. In Wakely's case the intervascular areas were highly cellular, creating an appearance which the author felt was consistent with angioblastoma. Although further pathologic studies must be made before definite conclusions can be drawn regarding the anatomic structure of the tumor, it appears as if it may consist of capillaries, cavernous spaces, arteries or veins and possibly even proliferating angioblasts. Furthermore, the clinical symptoms in certain cases suggest that there is an associated intracranial vascular lesion in addition to the communication with the sagittal sinus.

TABLE 3.—*A Case of Sinus Pericranii* *

Case	Sex	Age	Symptoms and Findings
8	F	4 yr.	Enlarging tumor of midline of forehead containing venous blood. It was obliterated by injections of a sclerosing solution

* A report of this case was published previously (Peyton, W.: Minnesota Med. **21**: 500, 1938).

CAVERNOUS ANGIOMA

Introduction.—Cavernous angioma is a vascular lesion comprised of closely packed dilated vascular spaces which are not separated by brain tissue. It is often referred to as cavernoma. Dandy [7] in reviewing the literature discovered 44 cases of what he considered to be cavernoma. Other authors, however, have felt that Dandy [7] included a number of vascular tumors which were not cavernous angioma but were actually other forms, such as racemose angioma and telangiectasis (Bergstrand and co-workers,[3] among others). Many authors have recorded

57. Amsler, C.: Frankfurt. Ztschr. f. Path. **11**:254, 1912.
58. Anders: Beitr. z. path. Anat. u. z. allg. Path. **64**:540, 1918.
59. Kallenberger, W.: Virchows Arch. f. path. Anat. **180**:130, 1905.
60. Kaufman: Zentralbl. f. Gynäk. **37**:209, 1897.
61. Orth, J.: Lehrbuch der speciellen pathologischen Anatomie, Berlin, A. Hirschwald, 1887.
62. Fisher, B.: Beitr. z. path. Anat. u. z. allg. Path. **27**:484, 1900.
63. Pott, P., cited by Hahn.[65]
64. Stromeyer: Deutsche Klin. **11**:160, 1850.
65. Hahn, E.: Arch. Surg. **16**:31, 1928.
66. Mueller, A.: Klin. Wchnschr. **49**:1372, 1912.

cases which have been generally acceptable—for example, Lorenz,[67] Hadlick,[43] Baum,[32] Stief,[68] Dandy,[7] Schmidt,[30] Rossolimo[69] and Bergstrand and his collaborators,[3] as well as others.

The literature on cavernous angioma contains a confusing number of terms, primarily because many of the authors have not understood the basic structure of tumors of this type. Yates and Paine[70] regarded what appeared to be a cavernous lesion as an arteriovenous angioma because they were able to inject it after death through its arterial supply. Cushing and Bailey[1] confused cavernoma with angioblastoma, regarding some examples of the latter as representing a cavernous type of angioblastoma. In none of their cases, however, was a true cavernous tumor described. Lesions of this type have also been placed under the heading of telangiectasis (Michael and Levin[27]).

TABLE 4.—*Cases of Cavernous Angioma Studied in the Departments of Neuropsychiatry and Pathology of the University of Minnesota*

Case	Sex	Age, Yr.	Symptoms and Findings	Gross Appearance	Location
9	F	36	Jacksonian epilepsy, hemiplegia, cranial bruit; intellectual deterioration	Intracerebral spongy tumors comprised of closely packed dilated and thin-walled vessels	One large and 3 small tumors within cerebrum; 1 within cerebellum
10	M	62	Jacksonian epilepsy, hemiparesis, aphasia, increased intracranial pressure	Wedge-shaped tumor made up of large dilated blood vessels within brain	Left frontoparietal region
11	M	10	Increased intracranial pressure, somnolence, obesity, polyuria, failing memory	Spongy vascular tumor within ventricular system producing internal hydrocephalus	Third ventricle and hypothalamus

Cavernous angioma produces no characteristic symptoms; in many instances it is entirely silent, while in others it is manifest in a variable picture of recurrent convulsive or focal phenomena. A cranial bruit is a rare finding, but intracranial hypertension is not uncommon.

Gross Pathology.—In the literature, cavernous angioma is generally described as being situated deep within the brain substance, but in all the cases tabulated here it reached the brain surface, and in 2 cases the overlying surface was covered with enlarged tortuous vessels. In the already published cases the tumor was located in order of frequency within the frontoparietal region, the pons, the vicinity of the third ventricle and the occipital lobes. In the cases tabulated here the tumor was found in the cerebral hemispheres, the third ventricle and the cerebellum, respectively. Cavernous angioma is usually single (cases 10 and 11), but occasionally it may be multiple and widely disseminated (case 9). Other instances of multiple lesions were reported by Riddoch,[71] Federoff and Bogorad[72] and Kufs.[37]

The tumor itself is reddish brown or bluish and consists of large thin-walled vascular spaces which are closely packed. It is, as a rule, compressible and spongelike, especially when the cavernous vessels are large. The individual vascular spaces vary considerably in size and may be so congested as to obscure the cavernous vessel walls, thereby presenting a superficial resemblance to an intracerebral hemorrhage. The lesion may be quite sharply circumscribed or may merge gradually with the neighboring parenchyma, the vessels in these regions being separated by nerve tissue, in contrast to the observation within the body of the cavernoma.

The lesion replaces the involved area of the brain and often produces atrophy of the regional tissues. This atrophy may in turn create secondary dilatation of the adjacent ventricle. Occasionally cavernoma protrudes into a ventricle, where it obstructs the outflow of cerebrospinal fluid, thereby producing obstructive internal hydrocephalus (case 11). Although rare, there are authentic cases in which vessels in a cavernoma have ruptured with resultant cerebral hemorrhage (Bergstrand and his associates[3]).

Microscopic Anatomy.—The histologic appearance of cavernous angioma is constant. The tumor is composed entirely of dilated vascular spaces filled with blood. Since there is no cerebral parenchyma separating the vessels, their walls are in direct contact with one another. The thin walls are comprised solely of fibrous connective tissue, which is generally largely hyaline. The cavernous lumens are lined with a single layer of flattened endothelium which never shows any significant proliferative changes. Elastic and smooth muscle fibers are almost never observed (cases 9 and 11). Case 10, however, was an exception, for even in the most classic cavernous regions an occasional vessel wall revealed a very thin and delicate elastic membrane adjacent to the intima, as well as a few smooth muscle fibers. Vascular calcifica-

67. Lorenz, F. O.: Cavernöses Angiom des Rückenmarkes, Inaug. Dissert., Jena, B. Engau, 1901.

68. Stief, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:181, 1924.

69. Rossolimo, G.: Neurol. Centralbl. **15**:714, 1896.

70. Yates, A., and Paine, C. G.: Brain **53**:38, 1930.

71. Riddoch, G.: Proc. Roy. Soc. Med. **24**:382, 1931.

72. Federoff, H., and Bogorad, F.: Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:497, 1924-1925.

tion is common (cases 9 and 11), and thrombosis of the cavernous spaces occurs (case 10).

Around the periphery of the lesion certain vessels which are separated by brain tissue may have arterial or venous structure. These probably represent the afferent and efferent vessels of the tumor. The nearby brain tissue often undergoes regressive alterations and even actual softening with concomitant reactive gliosis (case 11).

VENOUS ANGIOMA

Introduction.—Venous angioma is a tumor of the brain comprised of a congeries of vessels structurally resembling veins. Under this title only those venous tumors extending deep into the brain parenchyma are considered; those limited to the meninges covering the cerebral tissues are correctly discussed later as angiomatous meningioma. Such a distinction was usually not made in the literature.

Largely because of the conflicting viewpoints regarding the structure of venous angioma, a rather redundant and confusing nomenclature has appeared in the literature. A few examples of these titles are the following: "venous aneurysm," a name which was obviously unsatisfactory (Vincent and Heuyer [73]; Rienhoff [20]); "venous anomaly" or "plexiform angioma" (Dandy [7]); and "venous hamartoma" (Turner and Kernohan [13]). Very often tumors of this type are referred to as cirsoid angioma or rankenangioma. Completely inaccurate terms are frequently encountered, as in Christiansen's [74] case, in which a venous tumor was entitled cavernous angioma. The term "venous angioma" is the most descriptive name; however, the title "venous racemose angioma" also should be accepted because of its wide use.

Reports of cases have been surprisingly infrequent and often incomplete. The apparent rarity of this venous lesion may be partly explained by the atypical nature of the clinical picture, which rarely permits antemortem diagnosis, and the prolonged clinical course, which makes it most difficult to follow the case to its termination, when an autopsy could be performed. Examples of venous angioma have been reported by Cushing and Bailey,[1] Bergstrand and his associates,[3] Dürck,[75] Therman,[76] Orbison,[77] Dowling [78] and Wolf and Brock,[79] as well as many other authors.

The most frequent clinical manifestations are recurring subarachnoid hemorrhage and repeated apoplectic attacks. Much of the confusion regarding the symptoms results from the frequency with which cases of Sturge-Weber disease have been regarded as instances of venous angioma.

Gross Pathology.—The most classic variety of venous angioma is a wedge-shaped or cone-shaped lesion in which the base of the cone is in contact with the leptomeninges and the tip reaches the ventricle (fig. 2). An aggregation of intertwining vessels is usually observed on the surface overlying the involved area. When the tumor is small, it may extend only to the deeper sulci, in which case the surface of the brain may appear normal or may reveal only a few enlarged vessels resembling varices (case 12). Within the brain there is a tangled mass of large vessels, which are separated from each other by thin layers of cerebral tissue. The resultant appearance somewhat resembles a varicocele (Bergstrand and his collaborators [3]). In rare instances the vessels are less closely arranged, being more sparsely distributed over the involved area (case 15). Occasionally the superficial vessels may communicate freely with

TABLE 5.—*Cases of Venous Angioma Studied in the Departments of Neuropsychiatry and Pathology of the University of Minnesota*

Case, Sex, Age	Symptoms and Findings	Gross Appearance	Location
12 M 37 yr.	Increased intracranial pressure, meningeal irritation, aphasia, hemiplegia	Wedge-shaped vascular tumor within brain associated with sub-arachnoid and intracerebral bleeding and encephalomalacia	Rolandic region of cerebrum
13 M 34 yr.	Recurring episodes of meningeal irritation and stupor	Vascular tumor obstructing ventricular system and extending over cerebral base	Third ventricle
14 F 19 days	Spina bifida, paralysis of lower limbs, Arnold-Chiari deformity of cerebellum (removed surgically)	Surgical defect and internal hydrocephalus	Cerebellum
15 F 29 yr.	Headache, diplopia, writhing movements, extensor rigidity of limbs, ultimate coma	Large tortuous vessels within an intracerebral hemorrhage rupturing into ventricle; associated cerebral aneurysm	Thalamus
16 M 35 yr.	Patient found dead	Vascular tumor within brain	Right frontal lobe

73. Vincent, C. L., and Heuyer, G.: Rev. neurol. **1**:509, 1929.

74. Christiansen, V.: Les tumeurs du cerveau, Paris, Masson & Cie, 1921.

75. Dürck, H.: München. med. Wchnschr. **54**:1154, 1906.

76. Therman, E.: Arb. a. d. path. Inst. d. Univ. Helsingfors **3**:67, 1910.

77. Orbison, T. J.: J. A. M. A. **64**:1575, 1915.

78. Dowling, E.: Bol. y trab., Soc. de cir. de Buenos Aires **10**:589, 1926.

79. Wolf, A., and Brock, S.: Bull. Neurol. Inst. New York **4**:144, 1935.

the dural sinuses (Hyland and Douglas [80]). Cushing and Bailey [1] insisted that the afferent artery of venous angioma is never enlarged, but case 13 in my table 5 shows that this is not always true. The lesion may actually protrude into a ventricle and if large enough may actually fill the ventricle, producing obstructive hydrocephalus (case 13).

Venous angioma is not an expansile tumor; rather it replaces the tissue of the involved area and not uncommonly causes definite atrophy of the region which may be evidenced by considerable dilatation of the nearby ventricle (case 12) and a pool of fluid overlying the shrunken cortex (Dandy [7]). Not infrequently some bleeding results from the tumor, which is most commonly evidenced by a thin layer of subarachnoid blood. Larger hemorrhages also occur either intracerebrally or into the ventricles (cases 12 and 15). Areas of encephalomalacia may be found adjacent to the tumor.

Microscopic Anatomy.—Most of the vessels in venous angioma structurally resemble normal veins. In rare instances the tumor may consist of venules (case 14) but never of arteries or arterioles, although a few arterioles may be present in scattered areas throughout the tumor. The vessels are usually irregular and bizarre in shape. Their walls are relatively thin but may show considerable variation. Occasionally, however, scattered vessels may present thick walls, while others may reveal marked irregularity within the circumference of a single structure.

The structure of a single vessel is usually constant. The innermost layer consists of a single flat endothelial lining, often associated with a delicate elastic membrane. This endothelium may undergo localized proliferation, producing finger-like projections into the lumen of the vessel. The elastic lamina, although forming fine reduplications, is usually not prominent and is often incomplete or even absent. The principal mural element of the vessels of these tumors consists of fibrous connective tissue, which underlies the endothelial and elastic laminas. These elements are generally of moderate thickness and may be intermixed with a few smooth muscle fibers. However, a prominent muscular layer does not occur in vessels regarded as venous in nature.

The cerebral parenchyma separating the vessels and surrounding the lesion manifests rather marked changes such as demyelination, degenerative alterations of nerve cells, gliosis, encephalomalacia and occasionally hemorrhage.

A number of investigators in reporting on the morphologic anatomy of tumors of this type regarded many of the thin-walled vessels, even those without a well formed lamina muscularis, as arterial in structure merely because a thin elastic membrane was observed. Bergstrand and his collaborators [3] maintained that the vessels were so abnormal that it was impossible to ascertain whether or not they were arteries or veins. That the vessels are abnormal is obviously true; however, in the cases tabulated here it was not difficult to determine the more specific nature of the vessels. Therefore, only the lesion which is composed of vessels principally of venous structure should be regarded as venous angioma.

ARTERIAL ANGIOMA (RACEMOSUM)

The name "arterial (racemose) angioma" refers to a vascular tumor consisting exclusively of a conglomeration of coiled arteries. Simmonds [18] favored the name "angioma arteriale serpentinum." Since the title "arterial angioma" has often been employed for lesions containing veins as well as arteries, most of the cases published in the literature actually were cases of arteriovenous angioma. In order to establish the diagnosis of angioma arteriale, it is necessary to prove that the afferent and efferent vessels as well as those comprising the tumor all have arterial structure. If such a criterion is followed, it is questionable whether such a lesion can be found (Bergstrand and his associates [3]), although its occurrence constitutes a theoretic possibility.

ARTERIOVENOUS ANGIOMA

Introduction.—Arteriovenous angioma is a vascular tumor comprised of a tangled plexus of vessels resembling both arteries and veins. A multiplicity of often ambiguous and confusing terms have been employed in the recording of cases. Lesions of this type have been referred to as arterial angioma (Cushing and Bailey [1] and others). Such a name, however, implies that they are comprised entirely of arteries. They also have been designated as arteriovenous aneurysm (Bergstrand and his co-workers,[3] Dandy [7] and others); however, this title is more correctly used in describing the traumatic fistula between the internal carotid artery and the cavernous sinus, which is not considered in this review. Other terms have also been suggested such as "aneurysmal angioma" (Craig [81]), "arteriovenous hamartoma" (Turner and Kernohan [13]), "cirsoid aneurysm" (Uiberall [82]) and

80. Hyland, H. H., and Douglas, R. P.: Arch. Neurol. & Psychiat. **40**:1220, 1938.

81. Craig, W. M.: Am. Heart J. **17**:40, 1939.

82. Uiberall, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:863, 1930.

many others. A few extremely confusing terms have been encountered such as "angioma anastomoticum," "varix arteriale," "varix aneurysmaticus" and "rankenaneurysm." Although the term "arteriovenous angioma" rarely appears in the recorded publications, it seems the most consistent with the pathologic structure and therefore should receive preference over other titles. It should also be mentioned that even though a rather large number of cases have been recorded, in very few of the descriptions has the anatomic structure been stressed.

The most characteristic clinical picture consists of convulsive seizures associated with focal symptoms recurring for many years. Contrary to the generally accepted conception, a cranial bruit and increased intracranial pressure are not common findings. Moreover, roentgenographically demonstrable calcification is more common within lesions of this type than in purely venous lesions.

TABLE 6.—*Cases of Arteriovenous Angioma Studied in the Departments of Neuropsychiatry and Pathology of the University of Minnesota*

Case, Sex, Age	Symptoms and Findings	Gross Appearance	Location
17 M 26 yr.	Deformed head, obesity, hypoplastic genitalia, strongly pulsating carotid arteries, optic atrophy, exophthalmos, positive Babinski signs, cerebellar symptoms, right hemihypesthesia	Very large tortuous vessels coursing diffusely over surface of brain and along ventricles; large expansile vascular tumor producing obstructive internal hydrocephalus	Cerebellum
18 F 56 yr.	Petit and grand mal convulsions, attacks of aphasia, right hemiparesis and hemianesthesia	Extensive wedge-shaped vascular tumor within brain substance compressing adjacent ventricle; part of tumor filled with hemorrhage	Greater part of left cerebral hemisphere above lateral ventricle
19 F 46 yr.	Grand mal convulsions, temporal fits, emotional and neurotic disturbances and intellectual deterioration	Subarachnoid bleeding; large angiomatous vessels over cerebral surface; large intracerebral hemorrhage containing numerous large angiomatous vessels	Left temporal lobe
20 M 57 yr.	Right-sided jacksonian epilepsy, hemiparersis, hemihypesthesia, aphasia	Large vascular tumor within brain containing diffuse hemorrhage which had extravasated into subarachnoid space and ventricles	Left parietal and occipital regions

Gross Pathology.—Arteriovenous angioma occurs most commonly in the cerebral hemispheres and only rarely in the cerebellum (case 17). In appearance the lesion is so similar macroscopically to venous angioma that a differential diagnosis cannot be made by gross examination alone. Like the venous, the arteriovenous tumor often occurs as a wedge-shaped lesion extending deep into the brain parenchyma. Although it frequently only replaces the involved tissue, resulting in atrophy of the region, in certain instances it behaves as an expansile growth compressing the surrounding structures (case 17). This occasional expansile nature is not encountered in venous angioma.

As a rule, the tumor is confined to one region of the brain (case 19) but may in certain instances extend throughout a cerebral hemisphere (case 18). Usually the entire surface of the involved region is covered with a dense plexus of angiomatous vessels. Not infrequently large abnormal vessels are observed over extensive areas of the brain surface not directly related to the principal vascular tumor. These vessels as well as those overlying the angioma itself often connect with enlarged tortuous vessels situated over the basilar structures. The latter vessels, in rare cases, may course along the optic nerve to reach the orbit and even the retina, according to Heitmüller,[83] Kreutz,[84] Rotgans and Winkler [85] and others. Exophthalmos may result, as in case 17. Occasionally in cases of arteriovenous angioma, large tortuous angiomatous vessels are observed involving the scalp. A moderate degree of dilatation and hypertrophy of the artery supplying the region involved by the angioma occurs more frequently in the arteriovenous than in the venous tumor.

Some portion of the angioma is usually in contact with one of the ventricles, occasionally producing considerable compression and even obstruction of the involved portion of the ventricle. Obstructive hydrocephalus may result in this way, but more frequently ventricular dilatation eventuates from the diffuse parenchymal atrophy. At times large angiomatous vessels may be observed coursing along the ventricular walls at a great distance from the main lesion (case 17).

In many cases some form of intracerebral hemorrhage eventuates from the rupture of one of the angiomatous vessels (cases 18, 19 and 20). Bleeding may be so extensive as to obscure much of the vascular nature of the tumor, creating the appearance of a cerebral hemorrhage (cases 18 and 19). Subarachnoid and intraventricular bleeding are both common. Occasionally the rupture of a cerebral hemorrhage into a ventricle produces a cyst communicating with the ventricle (Sorgo [86]). Grossly visible vascular calci-

83. Heitmüller, G. H.: J. A. M. A. **42**:648, 1904.
84. Kreutz, A.: Wien. med. Wchnschr. **53**:1726, 1903.
85. Rotgans, J., and Winkler, C.: Anevrysme racémeux de la pie-mére de l'hémisphere gauche. Exophthalmie pulsatile à droite. Trépanation. Hémiplégie transitoire. L'état actual de la chirurgie nerveuse, Paris, Chipault, 1902, p. 695.
86. Sorgo, W.: Zentralbl. f. Neurochir. **3**:64, 1938.

fication is encountered with much greater frequency than in cases of venous angioma.

Microscopic Anatomy.—This variety of vascular tumor is comprised of a collection of adult blood vessels which are separated from one another by brain tissue. The general histologic picture is similar to that described previously for venous angioma. Scattered throughout arteriovenous angioma, however, there are numerous vessels clearly resembling arteries. In 3 of the 4 cases tabulated here (17, 18 and 20), more than half of the vessels were arterial, while in only 1 case (19) were veins more numerous; yet even in this case vessels resembling arteries were prominent throughout the tumor.

As the vessels of arterial structure are the only morphologic feature by which arteriovenous angioma can be distinguished from venous angioma, the microscopic anatomy of only these vessels requires description. They tend to be round or oval but may be irregular in contour. Their walls are generally thick, with the individual vessels revealing little variation in their mural thickness.

The most characteristic feature of such a vessel is the presence of a relatively thick layer of smooth muscle comprising much of the wall. No vessel should be considered arterial without this type of tunica media. The lumen of the vessel is lined by a single layer of endothelium which may produce partial occlusion of the lumen through its proliferation. A prominent thick and wavy internal elastic membrane is usually present around the entire circumference of the vessel. It frequently reveals multiple reduplications. Such an elastic intima may be absent in an occasional arterial vessel and hence is of less value than the mucular lamina in determining the vessel's arterial structure.

Degenerative changes in the vessel wall are not prominent, but calcification of scattered vessels is the rule. The parenchyma surrounding the lesions and separating the individual vessels shows considerable degenerative alterations, such as disease of nerve cells, demyelination, encephalomalacia and gliosis. Extensive hemorrhages and large cerebral softenings are not uncommon.

ANGIOMATOUS MENINGIOMA

Introduction.—Angiomatous meningioma is a vascular tumor of the meninges comprised of various combinations of adult blood vessels, such as arteries, veins, cavernous spaces or capillaries. The lack of involvement of the underlying cerebral tissue differentiates this type of vascular tumor from the deeper, parenchymal angioma.

The literature is most meager as regards angioma of the meninges, only a few verified cases having been reported, such as those recorded by Worster-Drought and Ballance [87] and Globus.[8] Globus [8] was the only author to use the term "angiomatous meningioma." Cushing and Bailey [1] expressed the opinion that in most of their cases of venous angioma the lesion, which they called a superficial serpentine lesion, was restricted to the cerebral meninges; however, they were unable to prove this since none of their cases was studied pathologically. It was probably for this reason that angiomatous meningioma was not included in their classification.

Angiomatous meningioma may occur in Sturge-Weber disease as a concomitant lesion; however, in this condition it is not always present and hence is not considered of fundamental significance.

TABLE 7.—*Cases of Angiomatous Meningioma Studied in the Departments of Neuropsychiatry and Pathology of the University of Minnesota*

Case, Sex, Age	Symptoms and Findings	Gross Appearance	Location
21 F 65 yr.	Delirium, coma, vomiting, respiratory difficulty	Thick layer of subarachnoid hemorrhage	Surface of cerebellum
22 M 59 yr.	Symptoms of increased intracranial pressure, left internal squint, right ptosis and facial palsy, ataxia, pyramidal tract signs, dysphagia, respiratory difficulty	Extensive subarachnoid bleeding filled with a network of large tortuous vessels	Surface of cerebellum and right side of pons
23 M 54 yr.	Increased intracranial pressure, suboccipital headache, paresthesias of upper limbs, left cerebellar findings, signs of involvement of right pyramidal tract	Layer of extravasated blood containing large angiomatous vessels on brain surface	Right cerebellar hemisphere
24 M 76 yr.	Patient found dead	Firm, well circumscribed tumor attached to dura	Left cerebral hemisphere
25 F New born	Respiratory difficulty and cyanosis, with death occurring 12 hours after parturition	Tangled layer of vessels covering extensive area of brain surface	Medial surface of left cerebral hemisphere
26 F 28 days	Generalized hypotonia, tremor of right upper limb, respiratory difficulty, rapid downhill course	Extensive subarachnoid hemorrhage	Cerebellar surface

There is no characteristic clinical picture for angiomatous meningioma. Convulsive seizures plus various other manifestations may occur with cerebral lesions. Symptoms referable to the cerebellum, the brain stem and the cranial nerves are often observed with predominantly cerebellar lesions. A complicating subarachnoid bleeding may account for many of the clinical features.

Gross Pathology.—The angiomatous meningioma is observed on the surface of the brain as a plexus of large coiled blood vessels. Serial sections through the involved regions demon-

87. Worster-Drought, C., and Ballance, C. A.: Lancet **2**:125, 1922.

strate that the underlying parenchyma is not involved, thereby differentiating this vascular tumor from the deeper racemose angioma, which primarily involves the brain tissue and extends outward to reach the meninges. The angiomatous vessels may show a loose arrangement or appear as a dense vascular plexus completely hiding the underlying cortex (case 25). Large vascular channels often drain into the dural sinuses. The meningeal angioma may be confined to one region of the brain or may cover extensive areas of the cerebral surface. It may be found over the surface of the cerebrum, the cerebellum or the brain stem. In the cases tabulated here the cerebellum was the favorite location (cases 21, 22, 23 and 26).

A subarachnoid hemorrhage resulting from a rupture of one of the angiomatous vessels is a common complication (cases 21, 22, 23 and 26). This bleeding may be extensive and may so obscure the vascular tumor that the latter may be readily overlooked on gross examination (case 21). When such a subarachnoid extravasation occurs in the cerebellar region, it generally produces compression of the fourth ventricle and concomitant internal hydrocephalus.

A well circumscribed firm tumor of the meninges comprised of closely packed small blood vessels is an extremely rare form of angiomatous meningioma (case 24). Another rare variety is composed entirely of capillaries and is difficult to identify on gross examination (case 26).

Microscopic Anatomy.—Histologic study confirms the macroscopic observation that angiomatous tumor is confined primarily to the leptomeninges. A few vessels may be scattered along the subpial region of the underlying cortex, but the subcortical parenchyma is not involved. The structure of the vascular elements resembles that of arteries or veins; in other words, the microscopic anatomy is similar to that of venous or arteriovenous angioma except that the individual vessels are separated by loose connective tissue rather than cerebral parenchyma (cases 21, 22 and 23). Vessels of typical arterial structure were prominent in the cases tabulated here. In some instances the lesion is comprised of closely packed cavernous spaces (Globus [8]) or capillaries (case 26), thus simulating cavernoma or telangiectasis.

A rare form of angiomatous meningioma consists of a firm, well circumscribed lesion grossly. Microscopically it is comprised of a large number of small blood vessels situated close to one another (case 24). The walls of these vessels are greatly thickened with various degrees of associated occlusion of the lumens. In all the vessels profound hyaline degeneration is observed, and in a few extensive mural calcification. In some places the vessels are separated by thin bands resembling meningotheliomatous tissue, suggesting that such a lesion might have a mild transitional tendency toward the meningotheliomatous meningioma.

STURGE-WEBER DISEASE

Introduction.—Sturge-Weber disease consists of atrophy and calcification of the cortex of one cerebral hemisphere, which is generally associated with dilated or actually angiomatous vessels in the overlying meninges and an ipsilateral facial nevus. Even though many of the cases recorded in the literature were published as cases of cerebral angioma, it is questionable whether Sturge-Weber disease should be included with the vascular tumors, since either the vascularity of the meninges or the facial nevus may be absent. The most consistent finding is the calcified, atrophic cortex.

Sturge [88] published one of the first clinical reports in 1879. Later, Weber [89] noted the characteristic roentgenographic findings, which he erroneously ascribed to calcification of an intracranial angioma. Unfortunately, this misconception persisted in many of the subsequent pubcations and has occasioned much of the confusion in understanding the vascular tumors and malformations. Although the title "Sturge-Weber disease" has appeared frequently in the foreign literature, it has been almost absent from American publications, in which most of the cases are found recorded as cases of angioma. This error probably can be largely attributed to the popularity of the monographic study published by Cushing and Bailey, in which classic cases were regarded as cases of venous angioma. It was not until 1934 that Krabbe [90] proved beyond doubt that the roentgenographic picture was a reflection of the cortical calcification rather than of angioma. Krabbe suggested that the name of this condition be changed to "Kraft-Weber-Dimitri disease" in recognition of Dimitri's [91] beautiful descriptions of the roentgenographic picture. However, since the term "Sturge-Weber disease" has been so widely employed, it is questionable whether such an alteration is feasible.

There are now a large number of instances of Sturge-Weber disease recorded in the literature. As early as 1913, Hebold [92] reported 5 cases. In 1936 a review of the literature revealed re-

88. Sturge, W.: Tr. Clin. Soc. London **12**:162, 1879.
89. Weber, F. P.: Arch. Neurol. & Psychiat. **3**:134, 1922.
90. Krabbe, K. H.: Arch. Neurol. & Psychiat. **32**: 737, 1934.
91. Dimitri, V.: Rev. Asoc. méd. argent. **36**:63, 1923.
92. Hebold, O.: Arch. f. Psychiat. **51**:445, 1913.

ports of 68 examples of this disease (Greenwald and Koota [93]); however, the failure to recognize this condition, with the result that many cases were recorded under a variety of titles, makes it virtually impossible to discover all the recorded cases.

The outstanding clinical signs and symptoms consist of convulsive seizures, an ipsilateral facial nevus, contralateral hemiparesis and hemianopsia, ipsilateral exophthalmos, glaucoma and parallel, wavy lines of cortical calcification observed on roentgenograms of the skull.

Gross Pathology.—Few cases have been studied pathologically, and no material has been available to me for study. In the recorded cases the cerebrum showed atrophy involving only an isolated area or an entire hemisphere. There was a rather definite predilection for the occipital region; however, the case tabulated here was an exception since air studies revealed atrophy which spared only the occipital lobe. The atrophic areas appear shrunken, and the convolutions become

TABLE 8.—*A Case of Sturge-Weber Disease*

Case, Sex, Age	Symptoms and Findings	Roentgenologic Features
27 F 31	Port wine nevus of right side of face, left hemiparesis and hemihypesthesia, optic atrophy, convulsive seizures	Roentgenograms of skull and encephalography revealed atrophy of almost the entire right cerebral hemisphere, with wavy lines representing calcification of the cortical gray matter

narrow, hypoplastic and firm in consistency. Cut sections disclose marked diminution of the cerebral tissues eventuating in secondary dilatation of the regional ventricle. There is notable thinning of the cortical ribbon, in which macroscopic calcification is often visible. Occasionally large irregular nodules of calcification are observed (Krabbe [90]). Associated cerebellar atrophy is a rare concomitant occurrence (Hebold [92]).

The surface of the atrophic cerebrum is often covered with a congeries of enlarged angiomatous vessels or an actual angiomatous meningioma. In many cases, however, only a few dilated vessels are revealed; in a few cases there are no signs of any abnormal vascularity (Krabbe [90]; Kreyenberg [40]; Gerhard and Hansing [40]; Geylin and Penfield [94]). Ipsilateral buphthalmos or exophthalmos is a common finding. Also large dilated vessels may occur in the sclera (case 31).

Microscopic Anatomy.—The involved regions reveal a thin atrophic cortex in which there is relatively complete absence of neurons and axons. In addition, there is a prominent increase of fibrous astrocytes forming a dense interlacing meshwork of glial fibers. The small cortical blood vessels show extreme thickening and hyalinization of their walls and resultant narrowing of their lumens. Many of these vessels are completely calcified, with small calcific deposits situated in the intervascular tissue.

When an angioma is present, it is usually confined to the overlying leptomeninges. It is unusual for the angioma to invade the underlying cortex; however, such an occurrence was reported by Hassoi.[40] The structure of the angiomatous vessels generally resembles that of normal arteries or veins. Calcification of these vessels is not at all striking. Small heterotopias of cerebral tissue have been encountered in the leptomeninges by Bergstrand, Olivecrona and Tönnis.[3]

A vascular involvement usually resembling cavernous angioma may be found in the retina and the sclera of the diseased eye (Meller [95]), but others claim there may be no pathologic change to explain the ocular manifestations (Weber [89]).

The genesis of the cortical atrophy remains a moot point. While certain authors have considered this condition secondary to circulatory disturbances occasioned by the overlying angioma, others have regarded it as congenital aplasia of the cortex. The frequent occurrence of other congenital anomalies tends to favor the latter point of view.

ANGIOBLASTOMA

Introduction.—Angioblastoma is comprised of embryonic vascular elements and constitutes one of the most common intracranial vascular lesions. The tumor often occurs as a nodule in the wall of a cerebellar cyst. Because of the close macroscopic resemblance to cerebellar astrocytoma, these two lesions usually were not distinguished in the earlier publications. However, after the appearance of Lindau's [2] original article in 1926, angioblastoma has been widely recognized, with the result that a relatively abundant literature is now available.

The terms used, especially in the earlier records of cases, are most confusing. For some time tumors of this type were regarded as glioma (Roussy, Lhermitte and Cornil [96]; Cushing and Bailey [1]; Bassoe and Apfelbach [97]). Other

93. Greenwald, H. M., and Koota, J.: Am. J. Dis. Child. **51**:868, 1936.

94. Geylin, H. R., and Penfield, W.: Arch. Neurol. & Psychiat. **21**:1020, 1929.

95. Meller, J.: Arch. f. Ophth. **85**:255, 1913.

96. Roussy, G.; Lhermitte, J., and Cornil, L.: Ann. d'anat. path. **1**:333, 1924.

97. Bassoe, P., and Apfelbach, C. W.: Arch. Neurol. & Psychiat. **14**:396, 1925.

angioblastic lesions were referred to as cystic sarcoma (Cushing and Bailey [1]), sarcomatous hemangioma (Corten [98]), hemangiomatous cyst (Sargent and Greenfield [99]) and angioreticuloma (Roussy and Oberling [100]; Bergstrand, Olivecrona and Tönnis [3]). Not infrequently, even in recent articles, one encounters names of entirely different vascular lesions used for these neoplasms as, for example, "telangiectasis," "capillary hemangioma" or "angioma." Out of respect for Lindau's [2] pioneering studies, the lesion occasionally is spoken of as Lindau's tumor. Similar angioblastic tumors in other parts of the body generally are called hemangioendothelioma, a name which only occasionally is employed for the cerebellar tumors.

superfluous since lymphatic neoplasms of the nervous system are unknown. The term "angioreticuloma" is in keeping with the abundant reticulum of these tumors but is less widely known than the title "angioblastoma."

The clinical picture differs little from that of other cerebellar tumors. Treatment consists of early surgical removal of the mural nodule. Such a procedure frequently results in complete recovery of the patient with no recurrence of the tumor if it has been completely excised.

Gross Appearance.—Cerebellar angioblastoma has been described from the standpoint of pathology by a number of writers. A few of these are: Joseph [102]; Friedrich and Stiehler [103]; Bassoe and Apfelbach [97]; Lindau [2]; Cushing and

TABLE 9.—*Cases of Angioblastoma Studied in the Departments of Neuropsychiatry and Pathology of the University of Minnesota*

Case,	Sex	Age, Yr.	Symptoms and Findings	Gross Appearance	Location
28	M	40	Suboccipital cephalalgia, cervical rigidity, symptoms of increased intracranial pressure, slight paresis of left upper extremity; symmetric hydrocephalus on ventriculography	Mural nodule in a large cyst	Left cerebellar hemisphere
29	M	30	Deafness of right ear, spells of unconsciousness, occipital and nuchal pain, papilledema, anisocoria, paresthesias of left side of body, right hemihypesthesia, scattered irregularities of reflexes	Internal hydrocephalus; soft red tumor containing small cysts, well circumscribed	Upper part of medulla
30	F	38	Evidence of intracranial hypertension, occipital headache and tenderness, left exophthalmos, paresthesias of ulnar border of left hand	Solid reddish tumor nodule 2.4 cm. in diameter; large engorged vessels in involved region; internal hydrocephalus	Region of right cerebellar tonsil
31	F	12	Occipital headache, cervical rigidity, signs of increased intracranial pressure, anisocoria, tonic fits, dysmetria in right upper limb, positive toe signs	Firm red nodule 2 cm. in diameter in cyst wall	Anterosuperior part of right cerebellar hemisphere
32	M	45	Occipital cephalalgia, findings of increased intracranial pressure, tinnitus, vomiting, epigastric pain, ataxia with falling toward the right	Reddish cystic tumor mass	Region of cisterna magnum and lower fourth ventricle
33	M	28	Fronto-occipital headaches, advanced picture of increased intracranial pressure, ataxia, scattered changes in reflexes	Small reddish tumor nodule attached to cyst wall	Right cerebellar hemisphere (left hemisphere compressed)
34	F	25	Onset during pregnancy. Suboccipital pain, symptoms of elevated intracranial pressure, deafness of right ear, hyperactive reflexes, incoordination on right, ataxia	Grayish red neoplastic nodule in wall of a cyst	Left cerebellar hemisphere
35	M	23	Right-sided occipital headaches, choked disks with other signs of increased pressure, skew deviation of eyes, slurred speech, marked right-sided cerebellar manifestations	Small cyst containing a mural tumor nodule	Right cerebellar hemisphere

Cushing and Bailey [1] coined the term "angioblastoma." They noted that morphologically this neoplasm closely resembled the various stages that the vasoformative cells pass through during the early development of the vascular system as demonstrated by Sabin [101] in hanging drop preparations of the chick embryo. This observation gave the title "angioblastoma" a structural connotation, which most likely accounts for its universal acceptance. The prefix of the name "hemangioblastoma," which is often used, seems

Bailey [1]; Greenfield [104]; Bergstrand and his coworkers [3]; Levine.[5] Although angioblastoma may involve any region of the central nervous system, it shows a predilection for the hemispheres of the cerebellum (cases 28, 31, 33, 34 and 35). Another relatively common situation is the posterior portion of the cerebellar vermis (Cushing and Bailey [1]; present report, case 33). Occasionally, it is encountered in the brain stem as in case 29 and in cases reported by Berblinger,[105] Tannenberg,[106] Lindau [2] and many

98. Corten, M. H.: Frankfurt. Ztschr. f. Path. **29**: 693, 1921.

99. Sargent, P., and Greenfield, J. G.: Brit. J. Surg. **17**:84, 1929.

100. Roussy, G., and Oberling, C.: Presse méd. **38**: 179, 1930.

101. Sabin, F. R.: Anat. Rec. **13**:199, 1917.

102. Joseph, M.: Ztschr. f. klin. Med. **16**:347, 1889.

103. Friedrich, H., and Stiehler, H.: Deutsche Ztschr. f. Nervenh. **73**:158, 1922.

104. Greenfield, J. G.: Proc. Roy. Soc. Med. **24**:382, 1931.

105. Berblinger, W.: Arch. f. Ophth. **110**:395, 1922.

106. Tannenberg, J.: Ztschr. f. d. ges. Neurol. u. Psychiat. **92**:119, 1924.

others. In a few instances of angioblastoma of the brain stem or spinal cord, concomitant syringomyelia has been noted by Lindau,[2] Gaupp,[107] Pinner,[108] Schuback [109] and others. Angioblastoma of the cerebrum is a rare pathologic curiosity, but a few acceptable cases have been reported (Rochat [110]; Bielschowsky [111]; Berger and Guleke [112]; Schley [113]; Mariotti [114]). In many of the cases of intracerebral angioblastoma the lesion involves the regional meninges and hence may actually be meningioma (Barnard and Walshe [115]; Wolf and Cowen [116]; Keller [117]). Although more than one lesion is not common, multiple angioblastoma of the nervous system occasionally occurs, according to Koch,[118] Wersilow,[119] Schuback,[109] Möller,[120] Guillain and co-workers,[121] Davidson and coworkers,[122] Raney and Courville [4] and others.

The involved cerebellar hemisphere is often enlarged, compressing the brain stem and at times the opposite cerebellar hemisphere. The cerebellar tonsil may be forced through the foramen magnum. Aspiration of the involved fluctuating area generally yields a clear straw-colored fluid, which may quickly coagulate. Midline lesions are easily detected from the surface, since they spread the cerebellar tonsils. Enlarged, dilated blood vessels may be observed over the involved cerebellar surface. The fourth ventricle is always compressed, a condition eventuating in marked internal hydrocephalus. The floor of the fourth ventricle, however, is only rarely invaded (Zeitlin [123]).

107. Gaupp, J.: Beitr. z. path. Anat. u. z. allg. Path. **2**:510, 1888.
108. Pinner, A. W.: Arb. a. d. path. Anat. Inst. zu Tübingen **9**:118, 1914.
109. Schuback, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **110**:359, 1927.
110. Rochat, G. F.: Nederl. tijdschr. v. geneesk. **1**:1124, 1927.
111. Bielschowsky, M.: Deutsche Ztschr. f. Nervenh. **22**:54, 1902.
112. Berger, H., and Guleke: Deutsche Ztschr. f. Chir. **203-204**:104, 1927.
113. Schley, W.: Centralbl. f. allg. Path. u. path. Anat. **41**:337, 1928.
114. Mariotti, D.: Pathologica **28**:1, 1936.
115. Barnard, W. G., and Walshe, F. M. R.: J. Path. & Bact. **34**:385, 1931.
116. Wolf, A., and Cowen, D.: Bull. Neurol. Inst. New York **5**:485, 1936.
117. Keller, H.: Virchows Arch. f. path. Anat. **289**: 151, 1933.
118. Koch, F.: Ztschr. f. Kinderh. **59**:638, 1938.
119. Wersilow, W.: Neurol. Centralbl. **32**:340, 1913.
120. Möller, H. V.: Acta ophth. **7**:244, 1929.
121. Guillain, G.; Schmite, P., and Butrand, I.: Rev. neurol. **1**:420, 1932.
122. Davidson, C.; Brock, S., and Dyke, C. G.: Bull. Neurol. Inst. New York **5**:72, 1936.
123. Zeitlin, H.: J. Neuropath. & Exper. Neurol. **1**:14, 1942.

Cut sections of the cerebellum, as a general rule, reveal a large part of the hemisphere to be replaced by a large cyst containing clear yellow fluid. The walls of the cyst are smooth, showing no tumor except at the site of attachment of the mural nodule, which comprises the entire neoplasm. The tumor is either sessile or pedunculated, measuring only about 1.5 to 2.5 cm. in diameter. It is grayish to dark red and firm in consistency.

A less common form of angioblastoma consists of a solid, fairly well circumscribed tumor which is not associated with a large cyst (case 33). It generally contains multiple small cysts, which may be visible grossly (cases 29 and 32). In the rare instances in which angioblastoma occurs in the brain stem it may be solid or cystic. Cushing and Bailey's [1] division of the angioblastic lesions into cystic, partially cystic and solid varieties has little value since there are all sorts of transitional variations in the cystic structure.

Microscopic Anatomy.—Except for minor variations, the histologic structure of angioblastoma is remarkably constant. Small capillaries and occasionally a few cavernous spaces are disseminated throughout the tumor. These vessels are generally filled with blood. The intervascular areas are cellular and contain numerous tiny embryonic vascular spaces, which are usually empty (fig. 3). These tiny spaces are lined by either endothelial or actual neoplastic cells. The cells of the intervascular areas merge directly with those lining the vascular channels and appear to be growing from the outer surface of the capillary walls.

The typical neoplastic cell has an oval vesicular nucleus and often a nucleolus. The cytoplasm generally contains a few vacuoles. Sometimes the cytoplasm is extensive and filled with large vacuoles, giving the cell a foamy appearance. Cells of this type are referred to as pseudoxanthomatous or xanthic cells because of their resemblance to the foam cells characteristic of xanthoma (Lindau [2]; Turner and Kernohan [13]). Polariscopic studies suggest that the lipoid contained in these vacuoles is closely related to a cholesterol ester (Zeitlin [123]). It is most likely nutritional rather than degenerative in origin since it shows no constant relationship to areas of degeneration. Large foam cells were prominent in 4 of the cases tabulated here (28, 29, 31 and 32). In some areas of the tumor the nuclei may become pyknotic or appear elongated and fusiform. Multinucleated giant cells and large cells containing bizarre-shaped nuclei occasionally are observed.

Mitotic figures are seldom seen. A dense reticulum permeating the tumor is characteristic of these lesions and is best demonstrated by the Perdrau technic. The reticulum fibers encircle the capillaries and vascular spaces, sending branches into the cellular intervascular areas. Occasionally the reticulum is missing in the highly cellular areas. In certain regions of the tumor capillaries may be extremely prominent, while in other areas the structure is extremely cellular, with the vascular nature being indicated merely by the tiny embryonic spaces. Lesions in which cavernous spaces are predominant may be confused with cavernous angioma. However, the cavernous walls are more delicate than those of true cavernoma, and proliferating cells as well as embryonic vascular spaces are observed between the cavernous vessels. Also, areas of typical angioblastic structure are usually found in some portions of the tumor, proving conclusively that the lesion is angioblastoma rather than cavernoma.

Occasionally the neoplastic structure of certain regions of angioblastoma is distorted or even obliterated by a proliferation of fibrous connective tissue or fibrillary neuroglia (cases 28, 29, 33 and 34). The resultant morphologic alterations were termed sclerosing changes by Bailey and Ford.[24] Areas of necrosis (case 35), cystic cavities, edematous regions, collections of blood pigment or a marked proliferation of the endothelial lining of the larger capillaries (case 35) may sometimes be observed in angioblastoma.

The tumor is well circumscribed and often is circumvented by a zone of fibrous neuroglia (case 29). The wall of the cyst consists of glial fibers and contains no tumor tissue except at the site of attachment of the mural nodule. The cystic fluid is considered to be the result of transudation and resembles plasma in its chemical composition (Martin). The fluid quickly reforms after aspiration if the tumor nodule is not removed.

LINDAU'S (VON HIPPEL'S) DISEASE

Introduction.—This condition consists of an angioblastic tumor of the retina associated with single or multiple angioblastoma of the nervous system and various congenital lesions of other organs, such as cystic disease of the kidneys, the pancreas and the liver. Von Hippel's disease refers to an isolated angioblastic lesion of the retina, while the entire complex is termed Lindau's disease after the author who first popularized knowledge of the condition. Lindau[2] found that in 20 per cent of the recorded cases of von Hippel's disease there was evidence of associated neural lesions. Lindau's disease also has been called von Hippel-Lindau disease (Davidson, Brock and Dyke[122]) and Lindau-von Hippel disease (Craig, Wagener and Kernohan[124]).

The retinal lesion was first described by Fuchs[125] and Wood,[126] but Collins[127] was the first to recognize its true angioblastic structure. Although von Hippel[128] did not report this condition of the retina until 1903 and erroneously regarded it as an arteriovenous aneurysm, the disease still bears his name. Lindau's disease was first described by Schuback[109] but was not widely recognized until after Lindau's monograph. Cushing and Bailey[1] pointed out that Lindau overstressed the frequency of this condition and demonstrated that angioblastoma occurs much more often as an isolated cerebellar tumor. In the 8 cases of angioblastoma tabulated here there was no vascular tumor of the retina; however, in case 34 an associated cystic disease of the pancreas was found.

The clinical picture is most variable, being characterized by ocular and nervous system manifestations. Either a family history of the disease, which is obtained in about 20 per cent of the cases, or visualization of the retinal lesion is necessary for an antemortem diagnosis.

Pathologic Features.—A small tumor nodule which reveals angioblastic structure is found in the peripheral portion of the retina. A large tortuous artery and vein connect the neoplastic nodule with the optic disk. An associated cyst similar to that of the cerebellar lesion may produce a detachment of the retina. Secondary changes such as proliferation of connective tissue, organization of extravasated blood, adherence of the retina to the lens and calcification of the choroid may occur. These changes may obscure the vascular nature of the lesion and have been referred to as Coats's retinitis (Coats[129]). In contrast to the angioblastoma of the nervous system, the retinal neoplasm may undergo calcification and occasionally even ossification (Davidson, Brock and Dyke[122]).

By definition, single or multiple angioblastoma of the nervous system is present. The lesion of the nerve tissues possesses the same gross and microscopic features as the isolated lesion described in the previous section. Angioblastoma

124. Craig, W. M.; Wagener, H. P., and Kernohan, J. W.: Arch. Neurol. & Psychiat. **46**:36, 1941.
125. Fuchs, E.: Arch. f. Augenh. **11**:440, 1882.
126. Wood, D. J.: Tr. Ophth. Soc. U. Kingdom **12**: 143, 1892.
127. Collins, E. T.: Tr. Ophth. Soc. U. Kingdom **14**:141, 1894.
128. von Hippel, E.: Arch. f. Ophth. **59**:83, 1904.
129. Coats, G.: Arch. f. Ophth. **81**:275, 1912.

of the cerebellum is the most common but involvement of the brain stem and the spinal cord is not infrequent. Syringomyelia, hydromyelia or syringobulbia occasionally is found as a concomitant lesion, according to Davidson and his associates,[122] Craig and his associates[124] and others.

Cystic disease of the kidneys, the pancreas and the liver, as well as hypernephroma, is common. The hypernephroma does not metastasize. Other visceral lesions, such as an adenoma of the epididymis, a cavernoma of the liver (Koch[130]), an angioma of the kidney or a small cerebellar ependymoma, may occur (Craig and his coworkers[124]; Kernohan, Woltman and Adson[131]).

Although the cystic disease of the various organs has been regarded as very pathognomonic of this condition, such involvement of organs may occur in the absence of angioblastoma of the retina and the nervous system. Therefore, the angioblastic lesions are essential for a diagnosis of Lindau's syndrome.

ANGIOBLASTIC MENINGIOMA

Introduction.—Angioblastic meningioma is a rare form of meningeal tumor comprised of capillaries, embryonic vascular elements and an abundant stroma of reticulum. The term "angioblastic meningioma" was introduced by Bailey, Cushing and Eisenhardt.[132] They used this term interchangeably with "supratentorial angioblastoma" since their meningeal vascular tumors showed a predilection for the superior surface of the tentorium. More recently, however, the latter term has been used for the intracerebral as well as the meningeal angioblastic lesions. A few other titles occasionally have appeared in the literature such as "leptomeningioma piale" (Globus[8]), "malignant meningioma" (Bergstrand and his co-workers[3]), "capillary angioma" (Keller[117]), "perithelioma" (Borst[133]), "hemangioendothelioma" (Bruns[134]), "angiosarcoma" (Ribbert[17]) and "endothelioma angiomatosum" (Henschen[135]).

130. Koch, K.: Virchows Arch. f. path. Anat. **214**: 180, 1913.

131. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Arch. Neurol. & Psychiat. **25**:679, 1931.

132. Bailey, P.; Cushing, H., and Eisenhardt, R.: Arch. Path. **6**:953, 1928.

133. Borst, M.: Echte Geschwülste, in Aschoff, L.: Pathologische Anatomie, Jena, G. Fischer, 1913, p. 497.

134. Bruns, L.: Die Geschwülste des Nervensystems: Hirngeschwülste, Rückenmarks und Wirbelgeschwülste. Geschwülste der peripheren Nerven, Berlin, S. Karger, 1908, p. 19.

135. Henschen, F.: Ueber Geschwülste der hinteren Schädelgrube, insbesondere des Kleinhirn-brückenwinkels, Jena, Gustav Fischer, 1910, p. 84.

Since this variety of meningioma is rather rare and has been adequately described only in recent years, the literature regarding this lesion is relatively meager. Carefully verified cases have been published by Wolf and Cowen,[116] Tannenberg,[106] Bailey and Bucy,[136] Bailey, Cushing and Eisenhardt,[132] Corten,[98] Zeitlin,[123] Globus,[8] Bergstrand and his co-workers,[3] Bailey and Ford,[24] Courville and Abbot[26] and Patterson and Anderson.[137]

The clinical picture differs little from that of any other type of meningioma and depends largely on the location of the lesion. The clinical course is often rapid but may be prolonged. Although complete surgical removal is possible, postoperative recurrence is the rule.

Gross Appearance.—On gross examination alone, angioblastic meningioma cannot be differentiated from the more common varieties of meningioma. Generally the outer surface is firmly adherent to the dura but only in rare instances does the growth invade the overlying bone (Zeitlin[123]). The tumor usually assumes a globoid form but at times appears as a flat, plaquelike lesion. Although grossly the tumor appears to be well circumscribed, invasion of the adjacent parenchyma often occurs (cases 36 and 37). In most instances the tumor is firm or very fibrous in consistency. The cut surface varies from reddish brown to yellowish white (cases 36 and 37). Although gross examination may show striking vascularity, some of the more common forms of meningioma also possess copious vascularity.

Apparently any region of the brain may be involved by this type of meningioma. However,

TABLE 10.—*Cases of Angioblastic Meningioma Studied in the Departments of Neuropsychiatry and Pathology of the University of Minnesota*

Case, Sex, Age	Symptoms and Findings	Gross Anatomy	Location
36 M 46 yr.	Increased intracranial pressure, right homonymous hemianopsia, spastic paresis of right lower limb, right hemihypesthesia	Firm fleshy meningeal tumor 5 cm. in diameter grossly infiltrating adjacent cerebral cortex	Left temporal lobe
37 F 56 yr.	Headache, right hemiparesis and hemihypesthesia	Fairly well circumscribed meningeal tumor 5 cm. in diameter adherent to underlying cerebral cortex	Rolandic region of left cerebral hemisphere
38 F 62 yr.	Personality changes, headache, confusion, hyperactive reflexes, bilateral positive Babinski signs	Firm, well circumscribed globoid tumor 7 by 8 cm. in diameter adherent to dura	Orbital surface of right frontal lobe

136. Bailey, P., and Bucy, P. C.: Am. J. Cancer **15**:15, 1931.

137. Patterson, G. H., and Anderson, F. M.: Bull. Los Angeles Neurol. Soc. **5**:218, 1940.

the cases described in the literature as well as those tabulated here indicate that there is definite predilection for the cerebral convexities. The superior surface of the tentorium or the peritorcular region ranks next in frequency of involvement. The tumor also may be found in other locations, such as the regions of the inferior surface of the tentorium, the cerebellum, the olfactory groove (case 38), the cerebellopontile angle and the midline between the cerebral hemispheres, where it is adherent to the falx.

The large globoid form occasions a notable compression of the neighboring regions of the brain (case 38). Generally speaking, angioblastic meningioma is more invasive than the more frequently occurring, slower growing meningeal tumors.

Microscopic Anatomy.—The morphology of angioblastic meningioma is similar to that of cerebellar angioblastoma. In occasional cases the microscopic structure may be identical (Bailey, Cushing and Eisenhardt [132]). The meningeal tumor is composed of capillaries, cavernous spaces, proliferating endothelial cells or angioblasts and embryonic vessels lined by neoplastic cells. The cytoplasm of the tumor cells may contain a few vacuoles, but the characteristic large pseudoxanthomatous cells are not prominent. Not infrequently, the angioblastic cells tend to become elongated and spindle shaped throughout extensive portions of the tumor. Evidence of rapid growth is usually present as demonstrated by numerous mitotic figures (cases 36, 37 and 38). A few examples exhibited a striking variation in the size and the shape of the tumor cells as well as numerous giant forms containing large bizarre hyperchromatic nuclei. Wolf and Cowen,[116] Courville and Abbott [26] and others regarded this cellular variation to be indicative of high malignancy.

Other variations in the morphologic structure may occur. Scattered areas may closely resemble mesenchymal tissue (case 36). Also there may be a tendency to whorl formation, often with production of psammoma bodies, suggesting that the lesion is true meningioma (Bergstrand and Olivecrona [138]); however, these alterations might be attributed to independent inclusions of arachnoid (Wolf and Cowen [116]). Transitional lesions containing extensive areas of meningotheliomatous structure have been described by Cushing and Eisenhardt [25] and Courville and Abbott.[26] When considering these transitional neoplasms, however, one must be cautious since a slight angioblastic tendency is not infrequent in the more common types of meningioma.

Many of the variations in the microscopic structure of this tumor type may be the result of proliferation of the stromal elements. Bailey and Ford [24] referred to this alteration as a "sclerosing change." They felt that this sclerosing process accounted for the structural differences between the meningeal and the cerebellar angioblastoma.

Perdrau preparations demonstrate an abundance of reticulum throughout this tumor. The reticulum outlines the vessels and sends a network of branching processes into the intervascular regions. In those areas comprised of elongated fusiform cells the intervascular branches may be absent, with reticulum being observed only around the vascular channels (case 37).

ANGIOSARCOMA

The term "angiosarcoma" is occasionally used to describe vascular tumors revealing histologic evidence of rapid growth (Ribbert [139]; Turner and Kernohan [13]). In a large number of cases primary sarcoma of the brain is highly vascular, with collections of tumor cells encircling the blood vessels. Such a structure has suggested the titles "perivascular sarcoma," "plexiform angiosarcoma" and "perithelial sarcoma" to Borst [133] and others. This high degree of vascularity led Globus [8] to regard all the sarcomatous tumors as vascular lesions belonging to the group of neoplasms he entitled leptomeningioma piale. However, in many cases primary sarcoma of the nervous system fails to show angioblastic activity with resultant embryonic vascular channels; therefore, it should not be considered to be a vascular neoplasm. The term "angiosarcoma" applies only to a rapidly growing mesodermal tumor of the nervous system presenting angioblastic structure.

In general, an angioblastic tumor showing sufficient characteristics to be considered as angiosarcoma occurs as a meningeal rather than as an intracerebral or a cerebellar lesion (cases 36, 37 and 38). Hence, if such a term were accepted, it would include essentially the entire group of tumors classifiable as angioblastic meningioma. However, a few tumors of the latter group which are free from any anatomic evidence of rapid growth would be excluded from the group described as vascular sarcoma. Thus, even though the angiosarcoma group would consist entirely of tumors classifiable as angioblastic meningioma, not all of the tumors classed as

138. Bergstrand, H., and Olivecrona, H.: Am. J. Cancer **24**:522, 1930.

139. Ribbert, H.: Geschwülstlehre fur Aerzte und Studierende, Bonn, Friedrich Cohen, 1904, p. 591.

meningeal angioblastoma would be included. In addition, structures on the borderline of cancer would be difficult to classify. If in the future angioblastic tumors of rapid growth are found within the cerebral parenchyma, they should be classified as angiosarcoma.

ANGIOGLIOMA

Introduction.—The term "angioglioma" was introduced by Roussy and Oberling [100] in 1930 to designate a tumor comprised of adult vascular and glial elements. These authors expressed the opinion that this lesion was a neoplastic entity representing a transition between angioma and glioma. Only a few cases have been recorded in the literature, since this variety of tumor has not been generally accepted. Of the more than 700 cerebral tumors histologically verified in the departments of neuropsychiatry and pathology of the University of Minnesota, only 1 revealed structure suggestive of this type of lesion (table 11).

TABLE 11.—*A Case of Angioglioma*

Case, Sex, Age	Symptoms and Findings	Gross Appearance	Location
39 M 25 yr.	Head injury, convulsive seizures, headache, intellectual failure, hallucinations, increased intracranial pressure and roentgenographic evidence of calcification in right frontal region	A diffusely infiltrating firm and rubbery tumor containing disseminated foci of calcification	Right frontal lobe

There are no diagnostic clinical features. The picture is that of a slowly growing tumor of the brain, the resultant symptoms and findings being appropriate for the region involved by the lesion.

Gross Pathology.—Angioglioma may occur as a nodular tumor attached to the wall of a cyst or as a poorly circumscribed solid type of lesion. The cystic variety presents an appearance resembling astrocytoma except that it more frequently contains grossly visible areas of calcification (Bergstrand and his co-workers [3]). The solid variety is observed as a diffusely infiltrative lesion similar in appearance to astrocytoma. The cerebral structures involved by this noncystic tumor are firm and rubbery and exhibit small focal deposits of calcium (case 39). While any region may be involved by angioglioma, it most commonly is found in the cerebellum, where it occurs as a cystic tumor. In the cerebral hemispheres it generally assumes the appearance of a diffusely invasive lesion. Rare cases of multiple angioglioma have been reported (Wolff and Donat [140]).

140. Wolff, K., and Donat, R.: Ztschr. f. urol. Chir. **43**:272, 1937.

Microscopic Anatomy.—Histologically, angioglioma is composed of angiomatous and glial structures. The glial elements as a rule are represented by fibrous astrocytes which commonly have produced heavy glial fibers (case 39). At times there may occur an admixture of astrocytes and oligodendroglia. In a few instances the glial component assumes the structure of spongioblastoma polare (Bergstrand and his associates [3]). In all cases small blood vessels representing the vascular component are abundantly disseminated throughout the neoplasm. The vessel walls are often thickened and infiltrated by calcific granules. The noncalcified vessels possess thick hyalinized walls containing neither smooth muscle nor elastic tissue. These mural alterations occasion various degrees of luminal attenuation, including complete occlusion.

This transitional form of tumor has been accepted as a nosologic entity by only a few authors and has been rejected by many. Bailey and Ford [24] suggested that such a structure eventuated from the replacement of the original cellular elements in angioblastoma by proliferation of its glial stroma. Turner and Kernohan,[13] however, preferred to regard it as angioma associated with a profound secondary glial reaction. It has also been suggested that this neoplasm merely represents a highly vascular form of glioma. However, if the vascular components are primary rather than secondary, angioglioma may well represent an entity. The occurrence of the typical anatomic structure of astrocytoma without any associated increase in vascularity in many areas throughout the tumor in the case tabulated here (39) suggests that angioglioma may represent merely a variation of astrocytoma rather than a distinct transitional form of neoplasm. Although the validity of the term "angioglioma" is questionable, I feel that the tumor which it designates should be included in studies of the vascular tumors until more material has been studied.

COMMENT

In a survey of the literature concerning the intracranial vascular tumors there was encountered a striking diversity of opinion regarding these lesions. The conflicting nomenclature made an accurate identification of the discussed lesion difficult. However, from this mass of conflicting opinions and titles, there has emerged a relatively clear concept of a few fundamental vascular processes, namely, those named angioblastoma and telangiectasis. Many authors have attempted to establish a simple classification of the vascular lesions by dividing them into angioblastoma, telangiectasis and angioma. The last

was supposed to be comprised of vessels of an adult type, but the details of its structural variations were poorly understood since it was studied mainly from the clinical manifestations. Descriptions of lesions with this designation were generally limited to what might be noted in a superficial inspection at operation since pathologic studies were rarely made. In numerous cases, therefore, it was impossible to determine whether a lesion such as a racemose angioma involved only the surface of the brain or extended deeply into the cerebral substance. As a result of this paucity of anatomic studies, many different types of vascular lesions were confused; for example, Sturge-Weber disease was regarded in some cases as venous angioma. In addition, a large variety of vascular lesions were omitted from supposedly complete discussions on this subject. The large number of widely conflicting classifications of the vascular tumors evidence the confusion in the published literature.

A careful morphologic study of the structure of the lesions in the cases tabulated in the foregoing pages permitted their being arranged into various groups according to their structure. The lesions in each of these groups possessed a definite type of structure, different from that of any of the other groups. Thus, each variety constituted a pathologic entity. In selecting the title for each type of lesion, a term consistent with the vascular structure as well as with the terms most widely used in the literature was favored.

Before attempting a classification of the vascular tumors, it might be well to list the various forms of these lesions and indicate briefly the groups and the microscopic features which characterize them and which, in my opinion, make them separate and independent entities.

I. Telangiectasis.
   1. A collection of dilated capillaries.
   2. The capillaries are separated by normal brain tissue.

II. Rendu-Osler disease.
   1. Multiple telangiectasis of the skin, the mucous membranes and various internal organs.
   2. Only occasionally it involves the nervous system.

III. Varix or varicosity.
   1. One or several relatively large dilated vessels of regular contour.
   2. The vessels contain thin walls comprised of an endothelial lining and a layer of hyalinized connective tissue.
   3. Cerebral tissue separates the varicose vessels.
   4. The varix may be situated within the brain or the meninges.
   5. It may rupture to produce intracerebral hemorrhage.

IV. Sinus pericranii.
   1. A midline vascular tumor of the scalp or the forehead.
   2. It communicates with the superior sagittal sinus.
   3. Occasionally there may be an associated intracranial angiomatous lesion.

V. Cavernous angioma or cavernoma.
   1. Closely packed cavernous spaces, situated adjacent to one another without intervening neural tissue.
   2. The cavernous walls are thin, being composed of an endothelial lining and a layer of hyaline connective tissue.

VI. Venous (racemose) angioma.
   1. A congeries of entangled vessels often extending from the brain surface into the underlying parenchyma.
   2. The mural structure of most of the vessels resembles that of veins.
   3. The vessels are separated by degenerated parenchyma.

VII. Arteriovenous (racemose) angioma.
   1. Similar to venous angioma except that vessels resembling arteries are prominent.
   2. The walls of the arterial vessels are composed of a fairly well developed muscular media and an internal elastic membrane.

VIII. Angiomatous meningioma.
   1. A plexus of enlarged vessels restricted principally to the leptomeninges.
   2. The vessels consist of arteries, veins, cavernous spaces or capillaries.

IX. Sturge-Weber disease.
   1. Atrophy and calcification of the cortex of a part or of all of one cerebral hemisphere.
   2. The involved cortex is often covered with an angiomatous meningioma.
   3. There may be a homolateral port wine nevus of the face.
   4. The atrophic cortex shows parenchymal devastation, glial repair and vascular calcification (no angioma).

X. Angioblastoma.
   1. It occurs most commonly in the cerebellum.
   2. It is often cystic (a nodule in a cyst wall).
   3. Structurally it consists of numerous capillaries separated by proliferating cells, producing embryonic vascular spaces.
   4. There is an interlacing network of reticulum throughout the tumor.

XI. von Hippel-Lindau disease.
   1. Angioblastoma of both the retina and the nervous system (essential lesions).
   2. There are often associated visceral lesions, such as cystic disease of the kidney, the pancreas and the liver.

XII. Angioblastic meningioma.
   1. It grossly resembles the more common types of meningioma.
   2. It is often invasive, manifesting rapid growth.
   3. Morphologically it is similar to other forms of angioblastoma.

XIII. Angioglioma?
1. A nodule in a cyst wall or a solid tumor.
2. It contains visible calcium deposits.
3. It is composed of glial and vascular elements.
4. There are numerous thick-walled vessels, which are often calcified and are embedded in glial tissue (usually fibrous astrocytes).

XIV. Arterial (racemose) angioma?
1. A tangled collection of coiled vessels.
2. All the vessels must display arterial structure.

Since a complete classification based on the different types of anatomic structure of vascular tumors or malformations has never been published, a comprehensive pathologic classification is needed. The simple listing of the various pathologic forms of vascular lesions presented here is adequate if the same term is always applied to the same vascular picture regardless of the clinical features. There are a number of ways to arrange the various types of vascular tumors in forming a classification. They are all more or less acceptable if they are based on the different types of anatomic structure of the lesions. The nosologic grouping which is the most consistent with both the gross and the microscopic nature of these lesions no doubt would furnish the greatest contribution toward an understanding of the pathology of the vascular tumors. The results of the present study suggest that the following classification is more closely correlated with the types of vascular structure (gross and microscopic) than the other possible arrangements.

PATHOLOGIC CLASSIFICATION OF THE INTRACRANIAL VASCULAR TUMORS AND MALFORMATIONS

I. Angiomatous lesions (comprised of adult vascular elements).
1. Parenchymal angioma.
(*a*) Telangiectasis (capillary lesion); Rendu-Osler disease.
(*b*) Parenchymal varix or varicosity (single or multiple).
(*c*) Cavernous angioma or cavernoma.
(*d*) Venous (racemose) angioma.
(*e*) Arteriovenous (racemose) angioma.
(*f*) ?Arterial (racemose) angioma.
2. Meningeal angioma.
(*a*) Angiomatous meningioma.
(*b*) Meningeal varix or varicosity: leptomeningeal varix, dural varix, sinus pericranii associated with intracranial angioma(?).
(*c*) Sturge-Weber disease associated with angioma of the meninges.

II. Angioblastic lesions (comprised of embryonic vascular elements).
1. Parenchymal angioblastoma.
(*a*) Lindau's disease (von Hippel-Lindau disease).
2. ?Angioglioma.

III. Miscellaneous vascular lesions.
1. Sinus pericranii that is mainly extracranial.
2 ?Angioglioma.
3. Sturge-Weber disease without angiomatous lesions.

In this classification a majority of the vascular tumors are divided into two main groups according to definite distinctions in their actual anatomic structure. One includes lesions comprised of blood vessels of an adult type and the other includes tumors composed of embryonic vascular elements. The third group is reserved for a few remaining conditions not definitely belonging in the foregoing sections. Then the two main groups are again divided into lesions of the meninges and lesions of the brain parenchyma. Lesions implicating both the meninges and the cerebral tissue are considered as parenchymal lesions since the extent of the neural involvement greatly outweighs the meningeal in significance. These steps are readily apparent except in a few instances, which are indicated by question marks. Sinus pericranii is classified in two different ways since it appears to be mainly extracranial in some cases and intracranial in others. Sturge-Weber disease when associated with angioma of the meninges is placed with the other angiomatous tumors of the meninges while Sturge-Weber disease without such vascular involvement is regarded as a miscellaneous or related condition. The tumors that have been called angiosarcoma are not given a separate heading since they all seem to be classifiable as angioblastic meningioma (see section entitled "Angiosarcoma," page 54).

This classification is submitted with the hope of stimulating a greater consideration of the pathologic structure in further investigations of the intracranial vascular lesions, thereby increasing understanding of the relationship between their clinical and their pathologic aspects. Only if the basic pathologic character is kept in mind will a clearer conception of the correlation between the clinical, the physiologic and the morphologic features of these lesions eventuate. Moreover, there is little doubt that continued inquiries of this kind will increase the ability of physicians to predict the structure of a vascular lesion from its clinical picture.

Book Reviews

A Symposium on Mammary Tumors in Mice. Publication of the American Association for the Advancement of Science no. 22. By Members of the Staff of the National Cancer Institute, National Institute of Health, United States Public Health Service. Edited by Forest Ray Moulton. Pp. 223, illustrated. Washington, D. C., 25; American Association for the Advancement of Science, 1945.

The Symposium consists of twelve papers contributed by ten members of the staff of the National Cancer Institute who have been engaged over several years in the study of tumors of the breast as these develop spontaneously or are induced experimentally in mice belonging to various highly inbred strains. The contributors, who write with the authority derived from a prolonged study of the various problems, have succeeded in their object, which, as stated by M. B. Shimkin in a "General and Historical Introduction," is "an attempt to collect, to evaluate and to synthetize so far as possible information concerning a specific neoplasm in a specific species of mammal. The major purpose of the symposium is to acquaint the workers in cancer research and those more casually interested in the field with the advances made in this problem . . ."

The first group, consisting of four papers, is concerned with the morphology of the murine mamma and of its epithelial neoplasms. A short paper entitled "The Cytology of Mammary Tumors" by A. J. Dalton describes mainly the Golgi apparatus. A second paper by the same author entitled "Histogenesis of the Mammary Gland of the Mouse" describes the reaction of the gland to various conditions, such as diet, hormones, pregnancy and lactation, as determined by studying the gland in whole mounts. A third short paper, on the vascular supply of the carcinoma of the mammary gland, by G. H. Algire and H. W. Chalkley is essentially an account of a technic for studying the vascular supply of this neoplasm when it develops either spontaneously or after transplantation. These three papers do not quite conform to the plan of the book since, interesting though they are, they are essentially accounts of original studies in limited fields. The fourth paper, however, entitled "Morphology and Histogenesis of Mammary Tumors," by T. B. Dunn gives a comprehensive account of the subject. Of particular interest is the comparison of the morphologic characters of spontaneous mammary tumors developing in inbred strains with the descriptions by the earlier workers who examined the spontaneous neoplasms arising in the mammae of mice of mixed parentage. The four papers are illustrated by excellent photomicrographs.

The next group, consisting of three papers, relates to the causes of mammary cancer in inbred mice. W. E. Heston's contribution on the genetics of mammary tumors records in detail the history and the character of the various inbred strains that have been developed, and discusses some of the results obtained from a study of these strains. This systematic treatise in which a worker intimately familiar with the subject has brought together all the relevant data scattered through the literature will be welcomed by all who are engaged in the experimental study of cancer. It is accompanied by a bibliography comprising nearly two hundred references. The statement on page 56 that "different types of tumors are inherited as separate characters" reads like a lapse of the pen. Are tumors inherited? Does it not mean that the various organs inherit a susceptibility to the development of neoplasms as separate factors? It might have been added here that the recognition of the limitation of an inherited susceptibility to one particular organ enabled Waaler, in Norway, and Wassink, in Holland, to reveal the existence in man of inherited factors in the causation of cancer of the breast.

The complex and fascinating story of the discovery of the so-called milk factor is fully and clearly told in a review of H. B. Andervont. Although the existence of this factor was recognized only ten years ago, no less than one hundred papers are quoted in the bibliography. The term "milk factor" seems now to have been replaced by the term "milk influence," and so one comes on a section with the curious title "Physical and Chemical Properties of the Milk Influence." From the evidence available at present Andervont argues that the milk influence suggests the action of an agent "belonging or related to the viruses." While indicating the similarities between the milk influence and the viruses, he recognizes the long latent period of the milk influence as a dissimilarity.

The discovery of the milk influence as a decisive factor in the causation of mammary cancer has greatly diminished the significance of the part formerly attributed to the estrogenic hormone. It appears now that this hormone is concerned mainly with building up mammary gland tissue on which the milk influence can act. But there is the apparent paradox that the development of cancers in other organs, e. g., the uterine cervix, in response to this hormone is not dependent on the milk influence. Even in the mamma itself cancer can be induced in the absence of the milk influence by the local application of chemical carcinogens such as methylcholanthrene. This complex subject is clearly set out in a paper by M. B. Shimkin entitled "Hormones and Mammary Cancer in Mice." But the significance of the fact that there are two different etiologic types of mammary cancer in mice should have received more emphasis than is given to it in this account or in the final paper by Shimkin. There arises now the question to which etiologic type the mammary cancer belongs that develops in mice of mixed parentage. This could be determined by testing for the presence or the absence of the milk influence in such mice. The mice of mixed parentage reproduce more closely the conditions responsible for the development of cancer of the breast in women than highly inbred mice. The fact that in inbred strains multiple mammary cancers are much more frequent than in mice of mixed parentage is an indication that such etiologic differences exist.

The degree to which the development of mammary tumors and their subsequent growth can be influenced by such environmental factors as diet, aging and climatic conditions is discussed by H. P. Morris. Some extravagant statements have been made in the literature concerning the influence of diet, but the author has succeeded in separating the grain from the chaff. In addition to a detailed account of the effect of diet on the development and on the growth of cancer this sec-

tion provides a variety of interesting and valuable data which hitherto were scattered through the literature. An example is the frequency with which synchronous multiple mammary carcinoma is found in mice of mixed parentage and in mice belonging to inbred strains. Thus, in the early work of Haaland in mice of mixed parentage 17 per cent of the cancerous mice had multiple carcinoma, while in the more recent observations on two different inbred strains multiple carcinoma was found in 66 and 61.5 per cent of all cancerous mice.

The relation between age and the incidence of mammary cancer in inbred strains receives detailed treatment in which a clear distinction is made between the crude data (the number of deaths from cancer at different ages) and the death rates calculated from these data. The irregularities appearing in the older age groups are due to the small number of animals alive in those groups and also to the shortness of the age periods, single months, into which the normal span of life of the mouse has been divided in this paper. In cancer statistics applying to man age periods of ten years are used as a rule. These correspond to periods of three months in the shorter life span of the mouse. If the mortality rates per thousand were recalculated for three monthly periods the results obtained would resemble even more closely the conditions existing in man, namely, an increase which is progressively rapid.

In the chapter on the chemistry of mammary tumors, J. P. Greenstein has succeeded in condensing a vast amount of information into six pages of text, an achievement that will be welcomed by nonchemists. In addition to the chemistry of the tumors, information is given on the chemistry of the tissues of tumor-bearing animals and on different strains of mice. The surprising fact emerges that the degree of activity of one ferment, the serum esterase, which shows considerable differences between various strains, can be altered by foster nursing, so that the fostered mice have an activity resembling that of the strains to which the foster mother belongs. Greenstein summarizes the results of these investigations in the generalization that the end results of all forms of neoplastic growth are tissues which are chemically similar. Enzymatically tumors resemble one another more than they resemble normal tissues and more than normal tissues resemble one another.

The experimental work on the therapy of cancer, so far as it has been studied on mammary cancer of mice, is critically reviewed by H. M. Ryer. It is surprising to find that no less than 800 substances of various kinds have been tested for their therapeutic effect. Most of these have yielded completely negative results, but in spite of this melancholy fact the paper, which must have entailed a laborious search through the literature, makes interesting reading. The data are summarized in a tabular form most useful for purposes of reference.

The Symposium ends with a paper by M. B. Shimkin entitled "Conclusions—Including Discussion of the Possible Implications for Man." It sums up clearly and succinctly the results that have been obtained from a study of cancer of the breast in inbred strains of mice. But when the writer passes on to a discussion of their implications he goes sadly astray. He states (page 220): "It is plain that the designations of 'benign,' 'precancerous' or 'malignant' are clinical terms necessary for pragmatic purposes of selecting a therapeutic procedure and establishing prognosis but not applicable to experimental work."

I cannot find either in the Symposium or in the experimental work on cancer as this is known to me anything that would justify this extravagant, one might almost call it reckless, statement. If it refers to the inability to demonstate a clearcut morphologic difference between cancerous cells and noncancerous cells or between precancerous and nonprecancerous conditions, it refers to difficulties long recognized by pathologists. B. Bloch, who was both a clinician and a pioneer in the experimental study of carcinogenesis and whose work helped to establish the conception of precancer, emphasized the fact that there may be no morphologic distinction between a precancerous hyperplasia and a nonprecancerous hyperplasia. Cancer cells betray their presence by their biologic activity, namely, their power of autonomous invasive growth. What the experimental work in cancer has accomplished is the demonstration that this power is possessed only by cancer cells and not by cells present in hyperplastic or precancerous tissues. I find it difficult to believe that Dr. Shimkin wants pathologists to discard the conception of autonomous invasive growth as representing the essential nature of cancer. Nor should pathologists ignore the vast amount of work on human cancer that has made it possible to establish correlations between the morphologic appearances and the biologic behavior of a tumor. Whatever the meaning of the sentence quoted may be, it is unfortunately phrased.

On page 214, attention is dawn to the fallacy of assuming that statistical correlation implies causal or other direct connection. The fallacy is cleverly illustrated by the wearing of skirts, which "would undoubtedly correlate strongly with the occurrence of mammary cancer, yet has no possible direct significance in the etiology of such tumors." On the very next page, however, reference is made to the statistical correlation between the increase in age and the increase of incidence of mammary cancer, and it is argued, "Age in itself therefore is a predisposing factor in mammary cancer in man." This view was generally held until the discovery of experimental carcinogenesis made it possible to test its validity. When young and old mice were subjected to the experimental test, the alleged greater susceptibility failed to manifest itself. The susceptibility was either the same for both or higher in the young animals.

As a general proposition the explanation of the higher incidence of cancer with increasing age must therefore be abandoned. How, then, can this feature of cancer be explained? One factor which contributes to this phenomenon is the long period of induction of cancer, which becomes increasingly prolonged as the strength of the carcinogenic stimulus is diminished. This point is of more than academic interest. One cannot escape from old age, but it is possible to prolong the period of induction. That makes it possible to push the onset of cancer more and more into the older age groups. Such a result, which may be described as a halfway house to the prevention of cancer, would constitute a great advance in the control of the disease. But its possibility is not likely to be recognized so long as old age is in itself considered to be an etiologic factor.

Since in the experimental investigation of cancer the mamma of the mouse has been used exclusively as a test object, this book with its collection and ordered presentation of so many relevant data is likely to exert considerable influence on oncologic thought. It is a "must" for every cancer worker and a "should" for every pathologist and clinician who wants to keep abreast of the rapid advances in knowledge of the biology of cancer. This detailed, if in parts critical, review is a sincere tribute to its importance.

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